RHEUMATIC DISEASES

BASED ON THE PROCEEDINGS OF
THE SEVENTH INTERNATIONAL CONGRESS
ON RHEUMATIC DISEASES

PREPARED BY
THE COMMITTEE ON PUBLICATIONS OF
THE AMERICAN RHEUMATISM ASSOCIATION

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PREFACE

This volume is prepared from the talks or abstracts of the talks that were presented at the Seventh International Congress on Rheumatic Diseases. In some cases certain papers were not included because of limited space, and in these cases the omitted material concerned is adequately covered by another paper. In other cases, however, papers had to be omitted from this volume because a copy of the talk was not made available to the Editorial Committee.

A great many fields of interest are served in these pages, and many points of view appear. Subject matter ranges from the histology and biochemistry of connective tissue to hormone therapy and physical methods of rehabilitation, and includes many discussions in such diverse areas as those of orthopedic surgery, psychogenic rheumatism, experimentally induced lesions and serologic studies.

The book is arranged in twenty chapters. The first chapter presents general information about rheumatic diseases. The second chapter deals with rheumatic fever. Chapters 3 through 6 present papers on rheumatoid arthritis and closely related syndromes. Chapters 7 and 8 present papers on fibrositis, psychogenic rheumatism and osteoarthritis, which need to be distinguished from rheumatoid arthritis. Chapters 9, 10, and 11 include information on the various approaches to treatment. Other less common types of rheumatic diseases are presented in chapters 12, 13, and 14. Laboratory and investigative studies are presented in chapters 15 through 20.

As a unified record of current thinking and practice by leaders in both clinical and research work, these papers will be of day-to-day value to the practicing physician and to the man in the laboratory. They will also serve in the future as a milepost of progress along a difficult road.

The material presented by the authorities from all over the world should be of interest to clinicians and investigators alike.

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GENERAL INFORMATION ABOUT RHEUMATIC DISEASES

A CONTROLLED INVESTIGATION INTO THE ETIOLOGY OF RHEUMATOID ARTHRITIS

L. S. P. DAVIDSON

ETIOLOGY

Various factors have been arraigned as causing or predisposing to rheumatoid arthritis. Lack of agreement on the relative importance of such factors is due to the fact that the opinions expressed by the majority of workers in the field of the rheumatic diseases are based on general clinical impressions and not on evidence founded on controlled experiments which will withstand critical statistical analysis.

The Scientific Advisory Committee of the Empire Rheumatism Council ac- [illegible]

mittee. It was decided that for each rheumatoid arthritis patient investigated a control person, either entirely normal and healthy or alternatively suffer- [illegible]

It was also decided to limit the patients investigated to individuals who had had the disease not more than five years, since it was felt that questions relating to the onset of the disease would be difficult to answer if the time interval from onset was longer.

DEFINITION OF ONSET

[illegible]

logically with those obtained from the patients with whom they were paired Many questions put to the patients related to the date of onset of the disease, and in the absence of a corresponding reference point in the controls, [illegible]

At the time of questioning he had not had the same time in which to develop

the symptoms of rheumatoid arthritis as had the patient. He might do so one month after the interview, i e, three months after tonsillitis. If this did happen and he could have been recorded, he would move from the control into the patient group.

To obviate this difficulty it was decided to fix, for the controls, a reference point in time to which the questions related, comparable to the date of onset of the patient with whom the control was paired. In other words, each control was allotted a date of onset defined as x years before the date of interview, where x equalled the duration of the disease in the patient with whom the control was paired

The 230 pairs of questionnaires used in the pilot inquiry were not entirely discarded from this analysis. They have been included in the study of those problems which do not involve the date of onset, particularly in the study of the symptomatology of rheumatoid arthritis.

The statistical analysis is therefore based on a total of 532 pairs of patient and control questionnaires. In 302 of these pairs the questions to the control relate to a point of time comparable to date of onset in the paired patient, in the remaining 230 no such comparable reference point was present and the information is of value only in the study of such aspects as do not involve the duration of the disease

Each patient and each control required from three to four hours for examination and questioning. The case records were then sent for analysis to Dr Lewis Faning, Statistician to the Committee. His first task was to ascertain whether the patients and controls were strictly comparable in regard to age, sex, civil status, social class, occupation, educational status, age when married, and duration of marriage at onset of disease. He reported that the patients and controls were entirely comparable in all these respects and hence any differences subsequently discovered in the investigation could not be ascribed to the above sociologic factors.

ETIOLOGIC FACTORS

Sex Incidences It is generally agreed that rheumatoid arthritis occurs more frequently in females than in males, but the reasons for this proneness of women to develop the disease are no more understood than the reasons underlying the increased liability of men to develop duodenal ulcer The corrected incidence of males to females in the Empire Rheumatism Council's series of 532 was 100 males to 162 females. In the Edinburgh series of 388 cases investigated from 1935 to 1940 it was 100 males to 209 females In both series the patients were mainly in-patients in hospitals In 400 cases investigated in Edinburgh between 1945 to 1948 who were out-patients the incidence was 100 males to 348 females. This ratio probably approximates the true sex incidence of the disease in Britain, since the figures for in-patients are influenced by various factors relating to admission to hospital.

Mean Age at Onset. The mean age at onset for the 532 patients in the Empire Rheumatism Council's series was forty-two years for males and forty-one for females. Almost identical figures were obtained for the 788 patients investigated independently in Edinburgh The information derived from these 1320 cases does not support the view commonly expressed in the literature that rheumatoid arthritis has a special predilection for young women Statistical investigation of the proneness to develop rheumatoid

arthritis showed that the risk of developing the disease increased progressively for males and single females with each age group from 15–24 to 45–54, for married women the risk increased up to the age of thirty-five and then remained stationary.

Psychologic Precipitating Factors. These are widely held to be of importance in the etiology of rheumatoid arthritis Statistical analysis of the frequency of occurrence of various precipitating psychologic factors within two years of the onset of rheumatoid arthritis showed that they occurred as frequently in the controls (39 per cent) as in the patients (38 per cent), moreover, 90 per cent of both patients and controls recorded none of the precipitating factors within three months of the onset of arthritis Hence the [illegible] t in

[illegible] that previous illnesses may predispose to rheumatoid arthritis in some manner not understood Accordingly the patients were questioned in regard to previous illnesses which had affected them at various age periods Forty-three specific diseases were listed in the questionnaire These illnesses included such diseases as rheumatic fever, scarlet fever, venereal diseases, allergic diseases, infectious diseases, and endocrine diseases

[illegible]

Infections There was evidence that some infections (excluding scarlet fever and rheumatic fever) occurred within three months of the arthritis more frequently in patients (19 per cent) than in controls (11 per cent). The difference between these figures is statistically significant A similar figure of 18 per cent for patients with a history of infections occurring within three months of onset was obtained in 780 cases investigated in Edinburgh No comparable figures for controls are, however, available In assessing the significance of the differences between 19 per cent and 11 per cent in patients and controls, respectively, it is necessary to bear in mind the following possible fallacy The patients with rheumatoid arthritis have been questioned by their doctors after the onset of arthritis about the occurrence of various factors believed to be of etiologic importance, e g, familial incidence, preceding infections, psychologic trauma, and have naturally given considerable time and thought to these matters The controls would be less likely to remember the various illnesses or emotional shocks which had occurred months or years previous to the date of interview Hence, throughout this report minor increases in the incidence of various factors in patients over controls should be accepted as being of etiologic importance with considerable caution and reserve If, however, the incidence of any factor is found to be equal to or greater in the controls than in the patients this may be taken as strong presumptive evidence that that factor is not of significance in the etiology of rheumatoid arthritis

The failure of this investigation to demonstrate any increased incidence of various diseases before the age of fifteen, after the age of twenty-five or two years before the onset of arthritis, and the finding that more than 80 per cent of the patients suffered from no infection within three months

of onset does not lend support to the view commonly expressed that patients with rheumatoid arthritis are endowed with some abnormal immunity mechanism which makes them unduly susceptible to disease or that any specific disease or infection antedating the onset of arthritis has been shown to be etiologically significant.

ALLERGIC DISEASES Since many authorities believe that rheumatoid arthritis is due to an abnormal response on the part of the patient to an antigen, it was decided to find out whether patients with rheumatoid arthritis suffered from allergic diseases (asthma, hay fever, urticaria, etc) more frequently than the rest of the population Statistical analysis has showed no differences in this respect between patients and controls. Moreover, a study of the incidence of allergic diseases occurring in the parents of 532 patients and 532 controls showed no evidence of any familial tendency to allergic diseases Approximately 5 per cent of parents and 1 per cent of siblings in both patients and controls gave histories of allergy.

ENDOCRINE DISEASES It is frequently stated that hyperfunction or hypofunction of various endocrine glands is of etiologic importance in rheumatoid arthritis The fact that such disorders were found to be present in less than 1 per cent of 302 patients specially investigated for this purpose *must finally dispose of such claims This finding is also of particular interest* in view of the remarkable therapeutic effects of cortisone (compound E).

Focal Sepsis At medical examination of 532 patients and controls, foci of infection were found in 22 per cent of patients and in 10 per cent of controls This incidence is much lower than is usually reported in the literature on rheumatoid arthritis Since no information is available as to the length of time focal sepsis had been present or whether it preceded or followed the onset of rheumatoid arthritis, its significance as an etiologic factor remains in doubt. The data on focal sepsis in this series were collected by a m
should
decide
enced
to focal sepsis in the ear, nose and throat.

One hundred cases of rheumatoid arthritis and one hundred control persons, comparable in regard to age and sex, etc, were investigated in the *Edinburgh Rheumatism Clinic by an experienced* ear-nose-and-throat surgeon who used a certain fixed standard of assessment for both groups in regard to the diagnosis of what constituted focal infection The incidence of foci in the ear, nose and throat in the two groups was identical, 43 per cent in patients and 43 per cent in controls. Since cases with only radio- ... were included in both series,
ess
ird
to a previous history of ear-nose-throat trouble in both groups A history of an upper respiratory tract infection within three months of the onset of rheumatoid arthritis was obtained in only eight patients. No significant *difference was found between patients* and controls from bacteriologic ex-

tion in the upper respiratory tract are present more commonly in pati

with rheumatoid arthritis than in other comparable members of the community

Familial Factors in Rheumatoid Arthritis. An investigation into the incidence of arthritis in relatives of patients and controls showed that (*a*) 7 per cent of the fathers of patients as opposed to 3 per cent of fathers of controls suffered from arthritis, and 15 per cent of mothers of patients as opposed to 9 per cent of mothers of controls suffered from arthritis; (*b*) of 2151 brothers and sisters of patients with rheumatoid arthritis, eighty-two (3 8 per cent) had arthritis, and of 2143 brothers and sisters of the controls, thirty-eight (1 8 per cent) had arthritis These figures are statistically significant and therefore lend support to the contention that a familial factor is of etiologic importance The relatively low incidence of a familial history of arthritis and the greater likelihood of the patients' remembering relatives afflicted with the disease as compared to the controls necessitates withholding any final conclusions on the matter until further investigations have been undertaken

Home Conditions Immediately Previous to Onset of Rheumatoid Arthritis Three hundred and two patients and a similar number of controls were asked ten questions to elicit the home conditions under which they lived No significant difference was found between the patients and controls as regards the proportions living in urban and rural districts, or the length of residence in the houses occupied up to the date of onset Over 70 per cent of patients and controls had lived five years or longer in their present homes There had therefore been an equal exposure to any deleterious or beneficial home condition, and in the majority of cases the length of residence had been sufficiently long to allow any etiologic factors associated with home conditions to produce a visible effect Statistical analysis

more frequently by the controls than by the patients In only one respect was there a statistically significant difference between the two groups, namely, 28 per cent of patients and 20 per cent of controls claimed that their houses were damp This difference, although greater than would be expected by chance, was very much less than most authorities would have

bear some etiologic relationship to rheumatoid arthritis. No evidence in

by the number of children born alive during the first five years of marriage Twenty-one patients out of twenty-two who were the victims of rheumatoid arthritis when they became pregnant stated that the disease improved during pregnancy, only to become worse in seventeen cases after parturition

Relation of Menstrual History and Menopause to Onset of Rheumatoid Arthritis. A change in menstrual history preceding the onset of arthritis

occurred in 9 per cent of 317 female patients The menopause (defined as one year before and one year after the total cessation of periods) had been reached by 115 of the 341 female patients. A time relationship between menopause and onset was recorded by twenty-eight patients (26 per cent). A comparison with the controls on these points would be meaningless In the Edinburgh series a relationship between menopause and onset was found in 14 4 per cent of 132 patients between the ages of thirty-five and fifty-four (menopause was defined as two years before and after cessation of periods), a figure actually lower than might have been expected by chance *An analysis of some 900 women—married, single and of different ages—* suffering from rheumatoid *arthritis, indicates that of all females suffering* from the disease, 10 per cent or less show any association between the onset of the disease and changes in the menstrual history, the development of the menopause or the termination of pregnancy within six months of the onset of symptoms. Accordingly, I feel that no satisfactory evidence is available in support of the view that any of these factors can be of etiologic importance.

Relation of Occupation to Rheumatoid Arthritis The design of this inquiry makes it unsuitable for assessing whether a specified occupation or trade might predispose to rheumatoid arthritis An analysis of occupations of 532 patients at various periods of life showed a remarkable similarity with the occupations of 532 controls A further analysis of the type of work engaged in on the basis of (*a*) indoor, manual or nonmanual, (*b*) outdoor, manual or nonmanual, and (*c*) housewives, showed no statistical difference between the type of work engaged in by patients and controls. Accordingly, this investigation failed to support the view that the type of occupation as described above is a factor in the etiology of rheumatoid arthritis

A controlled study was also made into the influence of the following additional occupational factors which are sometimes alleged to be of importance· posture at work, the nature of the work, monotonous or varied; the type of flooring, e g , wood or stone, wet or dry; and the provision of bath-
[illegible] hat any of these factors bore any
[illegible] An investigation into the tem-
[illegible] patients and controls worked
showed no significant difference between the two groups except in one respect, namely, 12 per cent of patients and 5 per cent of controls stated that they worked in cold temperatures, the difference persisting when the atmosphere was dry or humid. The difference of 7 per cent is statistically significant and lends some support to the view that there may exist some etiological relationship between cold and the development of rheumatoid arthritis.

Abnormalities of the Peripheral Circulation The frequency with which
[illegible] peripheral
[illegible] er these
[illegible] bnormal
peripheral vascular system was present prior to the onset of the disease Accordingly a series of questions was devised to elicit the incidence of ab-*normalities of the peripheral circulation* in patients and controls, and to determine whether such changes were present before or only after the onset Analysis revealed that peripheral vascular disorders were present in 55 per cent of 532 patients but in only 12 per cent of 532 controls Sweaty hands

and sweaty feet and cold fingers were present in 43 per cent, 36 per cent and 15 per cent of the patients as compared to 6 per cent, 3 per cent and 5 per cent of the controls, respectively This analysis therefore confirms the clinical impression of the frequency with which the peripheral circulatory changes are found in patients with rheumatoid arthritis When, however, an analysis was made as to whether such abnormalities were present before or only after the onset of arthritis it was found that they antedated the onset in a large majority of cases. Further, since their incidence in patients as compared to comparable controls was much greater than could be explained by chance, it is reasonable to infer that such disorders of the peripheral vascular system are in the nature of etiologic factors rather than clinical effects resulting from arthritis

Additional Findings. Statistical proof was also obtained that the clinical [illegible] of [illegible] in- [illegible] hat the involvement of joints tends to be symmetrical, and that cold and wet adversely affect the arthritis

* * *

RHEUMATISM—A NATIONAL PROBLEM

LORD HORDER

In the United Kingdom we still quote the British statesman who said that the health of its citizens is a nation's greatest asset If this cliché be accepted it follows that all diseases are, in a general sense, national problems

But there are certain diseases which are in some special sense "national" in their importance. They may require measures of control because they are contagious, like typhoid fever or smallpox They may be so lethal in their effects that if their incidence is on the increase and their causation is unknown, they are a menace to the very persistence of society, like cancer Or they may have an economic significance which is out of proportion to their seriousness as a threat to life

It is in this last category that we must place rheumatism as having a "national" significance

The main effects of rheumatism are pain and disablement I can't give you figures for pain, because pain can't be measured It can only be suffered But for disablement I can tell you some dimensions In Great Britain over 300,000 new cases of disabling rheumatism occur every year. That is counting insured persons only These are about one-third of the total population, so if we multiply this number by three we arrive at the figure of 1,000,000 as the number of sufferers in the whole country, or one in fifty of the population

The economic damage in sick pay, lost wages, cost of medical care, etc , is indicated by the calculation that, among the insured workers of England and Wales, a loss of £17,000,000 a year is incurred from this cause To multiply that figure by three would not be accurate, since allowance should

be made for a lower incidence in other sections of the population The *cautious figure of £25,000,000* may be advanced, and this does not take Scotland into account.

That this does not overstate the case is suggested by calculations made in comparable countries In the United States even more gloomy figures are put forward It has been computed that in Massachusetts there are more cases of chronic rheumatism than of heart disease, tuberculosis and cancer combined.

The reason why little or no serious attention has been paid to this problem, in face of such tragic figures as these, is probably that the mortality rate directly attributable to rheumatic disease is low. That is, of course, true only of chronic rheumatism Acute rheumatism, as the chief cause of heart disease, is indirectly a wholesale killer

A PLAN FOR NATIONAL ACTION

Eight years ago the Empire Rheumatism Council in the United Kingdom put forward a plan for national action in respect of the problem of rheumatism This plan had become the prototype of a scheme which was promised by the Government under the National Health Services Act, but which for reasons of economy, it has not so far been possible to put into operation

One difficulty had to be faced at the outset of the plan The number of doctors with special knowledge of rheumatic disease was limited Rather *than wait for the training of specialists to staff every Rheumatic Treatment* Center, it was decided to set up specialized centers, properly staffed and equipped and, working in coordination with these, subcenters designed to treat the average case but to refer other cases to the specialized centers

This scheme was consistent with our existing medical system, which assumes on the part of the general practitioner a sound knowledge of the principles of medicine and surgery and an acquaintance with the common types of clinical material The best resource of any sufferer, at least in the first instance, is the family doctor If we do not accept this we deny the *efficiency of our whole medical system*

While we can reinforce the general practitioner's knowledge by short postgraduate courses in rheumatism, we can also come to closer grips with the rheumatic problem by encouraging young specialists in this particular field.

Treatment of Children Turning to schemes of treatment, we have two distinct sets of material to deal with, the juvenile patient and the adult In the case of the former the Empire Rheumatism Council considered that the Rheumatic Scheme of the London County Council Medical Authority *provided an excellent model* The basis of this scheme is the routine inspection of all children at entrance and at three subsequent stages in their school life

Following this "basis" came three supervisory Rheumatism Centers, one for children with a history of acute or subacute rheumatism or chorea, one for children having symptoms suggestive of a mild rheumatic infection, and one for suspected cases awaiting diagnosis These centers are supplemented by rheumatism units for more prolonged treatment and oversight, and for ameliorating home conditions where necessary.

The scheme is local, but it might, and should, be national It is expensive but the money is wisely spent

Treatment of Adults It is in the treatment of the adult rheumatic sufferer that the work of the Empire Rheumatism Council has proved of value It has been estimated that less than 10 per cent of the total number of rheumatic patients in England and Wales obtained special treatment in the early stages of their disease Yet there was good evidence that the results of early treatment of these patients might be very helpful This was shown to be the case at Buxton and Bath, in three large London clinics, and in at least one rheumatism center in the United States

With the object of embracing this whole class of patients the Empire Rheumatism Council outlined the following machinery

SPECIALIZED TREATMENT CENTERS Specialized Treatment Centers would be set up on a regional basis at a teaching hospital of university status The functions of such centers would include the diagnosis and treatment of cases, of both in- and out-patient type, referred by local treatment centers, by other hospitals, or directly by private doctors, the education of the patient in "home therapy", the investigation of new methods of treatment referred from any competent source, the institution of postgraduate courses in the diagnosis and treatment of rheumatic diseases, the provision of visits by consultant specialists to local treatment centers within its region, the advising of local treatment centers in regard to staff and equipment, the training of physiotherapists in coordination with the Chartered Society of Physiotherapists, and cooperation in research into the causative factors of rheumatic disease

The chief desiderata of a Specialized Treatment Center would be, (*a*) facilities for enrolling a full staff of consultant medical and dental specialists, physicians and surgeons, including an orthopedic and manipulative surgeon, a dentist a gynecologist, a rhinolaryngologist, a pathologist and a radiologist, (*b*) in-patient accommodation, either on the site or within convenient access, and (*c*) association with a university medical school and a fully equipped and staffed laboratory and with an efficient roentgenographic department

A Specialized Treatment Center should have, in addition to the specialist physician in charge, a whole-time permanent medical officer with special experience in rheumatic disease, and a staff of qualified assistants, paid or voluntary The auxiliary staff should include workers in every branch of physical therapy, radiology, hydrology, and chiropody At least one of its members should have a full nursing qualification

Such centers should have additional "base" beds in one of the lesser regional hospitals, where long-term cases can be treated and rehabilitated

LOCAL TREATMENT CENTERS In every region having a Specialized Rheumatism Treatment Center there would be established Local (peripheral) Treatment Centers These should be in sufficient numbers and so situated as to provide in conveniently accessible places treatment facilities for sufferers The equipment of a Local Treatment Center might be arranged for from fifty to 250 patients a day Equipment should provide for massage and remedial exercises and for the simpler heat and electrical treatments Sites for treatment centers would be usually found at hospitals, pit-head baths, public baths, welfare premises of industrial enterprises, and other public or semipublic institutions These centers would be planned for out-patients

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only. In-patient treatment would be provided by arrangement with the Regional Treatment Center.

Regular skilled medical supervision is essential. The medical supervisor would not necessarily be a whole-time official in a small center, but employed half-time or even quarter-time, fitting in his duties with other practice, or preferably sharing his time between two, three or even four Local Treatment Centers This is preferable because he would thus gain more experience of rheumatism It is important, from every point of view, including economy, that every practitioner in charge of a Local Treatment Center should have, in addition to his standard medical skill, special knowledge of the diagnosis and treatment of rheumatic disease

Patients at a Local Treatment Center would be accepted only on recommendation of their doctor They would be, as regards special rheumatism therapy, under the control of its medical officer; as regards other health matters, they would remain under the supervision of their family doctor (*insurance practitioner or other*). *It would be necessary, however, that the* Medical Officer of the Local Treatment Center should have the decision as to whether a course of physical treatment was necessary and of what kind, to avoid resources being wasted.

It would be one of the functions of the Local Treatment Center to seek to educate the people with whom it came into contact as to faulty conditions of living—housing, diet, clothing, social habits generally—which are conducive to rheumatic disease, and to give commonsensible advice as to measures of preventive precaution

That is, in bare outline, a plan to give reasonable opportunities for relief to all sufferers The details of methods of administration would probably vary in various localities. It would not be useful to attempt to catalog them here.

The chief purpose of the plan is to divide patients into three sections. (*a*) that large section which, with a very brief period of institutional treatment and a sound course of education, would be enabled to carry on chiefly by simple home treatment but would be kept under supervision by periodic *visits to a Local Treatment Center or by visits of skilled social service* workers, (*b*) a further large section which could secure adequate treatment [illegible] neces-sary [illegible] which calls [illegible] alized Treatment Center.

It can be confidently estimated that the expense of such a system would represent an insignificant percentage of the yearly economic loss now caused by the large measure of neglect of adequate treatment of rheumatic disease

ABSTRACTS

MEDICAL CARE OF CHRONIC RHEUMATIC DISEASE IN ENGLAND AND WALES UNDER THE NATIONAL HEALTH SERVICE· ADMINISTRATIVE ASPECTS

E T. CONYBEARE

An accurate estimate of the number of patients likely to need medical care for chronic rheumatic disease in England and Wales under the National Health Service cannot be made.

For administrative purposes the health service is divided into three parts the hospital and specialist service, the local authority health service, and the general practitioner service The care of chronic rheumatism will be mainly the concern of the hospital and specialist service

For the administration of this part of the health service the country has been divided into fourteen geographical regions. Of the twenty-two hospitals with under-

In 1944 a special advisory committee recommended to the Minister of Health that, to promote research on the causes of rheumatic disease, all the university teaching hospitals should be asked to set up centers with specialized facilities for

for the study of chronic rheumatic disease along the lines recommended This means that in eight of the fourteen hospital regions, comprising over half the total population of the country, the medical care of chronic rheumatic disease remains

may be regarded as the chief administrative difficulty in developing better medical care for rheumatic patients under the British National Health Service

UNDERGRADUATE TEACHING OF THE RHEUMATIC DISEASES

HENRY F WRIGHT

moving pictures and television. It is suggested that undergraduate didactic

[illegible]

THERAPEUTIC CRITERIA AND RELATED AIDS IN RHEUMATOID ARTHRITIS†

CORNELIUS H TRAEGER AND ROBERT C BATTERMAN

This report summarizes recommendations for uniform therapeutic criteria in rheumatoid arthritis To prevent the inclusion of doubtful cases in reporting results, the following definition of rheumatoid arthritis is given, the definition closely follows that established by the American Rheumatism Association

Definition Rheumatoid arthritis is a systemic disease of unknown etiology, occurring at all ages It may be acute, subacute or chronic It may be reversible, especially in the early stages It is generally a chronic, progressive disease with joint involvement as the chief manifestation Ordinarily, it is polyarticular and usually symmetric The typical joint swelling presents a fusiform appearance. The affected joints are characterized by pain, stiffness, swelling and, many times, other signs of inflammation Subcutaneous nodules, tenovaginitis and muscular atrophy are fre-[illegible] an elevation of the erythrocyte sedimentation rate, and sometimes leukocytosis, anemia, fever, vasomotor imbalance, loss of weight and anorexia Although the course of this condition tends to be progressive, with exacerbations, it may be punctuated by spontaneous remission In early rheumatoid arthritis joint swelling may [illegible] doubtful case should be omitted from any therapeutic investigation

[illegible]

stages

Stage I, Early *1 No destructive change roentgenologically
2 Roentgenologic evidence of osteoporosis may be present.

Stage II, Moderate *1 Roentgenologic evidence of osteoporosis, with or without slight subchondral bone destruction, slight cartilage destruction may be present
*2 No joint deformities, although limitation of joint mobility may be present.
3 Adjacent muscle atrophy
4 Extra-articular soft tissue lesions, such as nodules and tenovaginitis, may be present

Stage III, Severe *1 Roentgenologic evidence of cartilage and bone destruction, in addition to osteoporosis
*2 Joint deformity, such as subluxation, ulnar deviation or hyperextension, without fibrous or bony ankylosis
3 Extensive muscle atrophy

† For the complete paper see Steinbrocker, O, Traeger, C H, and Batterman, R C· J A M A, *140* 659, 1949

* *The asterisk indicates criteria which must be present to classify a patient in any particular stage or grade*

4 Extra-articular soft tissue lesions, such as nodules and tenovaginitis, may be present

Stage IV, Terminal *1 Fibrous or bony ankylosis

[illegible]

out handicaps

Class II Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints

Class III Functional capacity adequate to perform only little or none of the duties of usual occupation or of self-care

Class IV Largely or wholly incapacitated with patient bedridden or confined to wheel chair, permitting little or no self care

The following criteria may be used for determining the response of rheumatoid activity to therapy

Grade I, Complete Remission *1 No systemic signs of rheumatoid activity (see definition)

*2 No signs of joint inflammation

*3 No evidence of activity in any extra-articular process, including nodules, [illegible]

*4 [illegible] than that associated with [illegible]

*5 [illegible]

6 Articular deformity, or extra-articular involvement due to irreversible changes, may be present

Grade II, Major Improvement *1 No systemic signs of rheumatoid activity, with exception of an elevated sedimentation rate and vasomotor imbalance

*2 Major signs of inflammation resolved, such as heat, redness of joints and of extra-articular involvement

*3 No new rheumatoid process of intra-articular or extra-articular structures

4 Minimum joint swelling may be present

5 Impairment of joint mobility associated with minimum residual activity may be present

6 Articular deformity, or extra-articular involvement due to irreversible changes, may be present

[illegible]

*3 No evidence of extension of rheumatoid activity into additional articular or extra-articular structures

4 Decreased but not minimum joint swelling present

5 Impairment of joint mobility due to residual inflammation may be present

6 Articular deformity, or extra-articular involvement due to irreversible [illegible]

[illegible] ns of rheumatoid [illegible]

[illegible] development of new sites of rheumatoid activity

*3 Roentgenologic changes indicative of progression of the rheumatoid process, excepting hypertrophic changes

4 In the presence of one or more of the above, improvement in other features, including a normal or lowered erythrocyte sedimentation rate, not significant

Whenever possible precision instruments, such as tape measure and goniometer, should be used in estimating the degree of swelling and motion for the purpose of reporting progress of the disease under therapy It is urged that an arbitrary time

limit be established for initial therapeutic response for each method of therapy, long enough to exclude the factor of spontaneous remission To avoid errors arising from misinterpretation of the natural fluctuations of the disease it is recommended that Minor Improvement (grade III) should not be considered significant and should not be included in any statistical survey of a therapeutic agent or procedure

RHEUMATIC FEVER

THE STREPTOCOCCAL ETIOLOGY OF RHEUMATIC FEVER

HOMER F. SWIFT

Many old observations, made frequently in the latter third of the previous century, that tonsillitis and scarlet fever often act as forerunners of rheumatic fever, were summarized in 1899 by Pribram,[1] and the recorded relationship between these two precursors and rheumatic fever, was found by him to vary between 2 and 85 per cent. A decade ago, Coburn[2] in the United States and Schlesinger[3] and Sheldon[4] in England redirected attention to this relationship, but there appeared several opponents of this thesis who based their opposition on the following observations: first, that frequently no hemolytic streptococcal infections are demonstrable bacteriologically at the time of onset of rheumatic fever or during its course; second, that many cases of streptococcal infections occur without being followed by rheumatic fever. The first objection could not be answered until data relating to hemolytic streptococci and their antibodies were better developed, the second is still a mystery.

CLASSIFICATION OF STREPTOCOCCI

Classification and differentiation of streptococci based on biochemical characteristics often yield little information concerning their antigenic capacities and relationships, hence immunologic correlation among the various strains encountered was usually impossible until Lancefield's system of classifying streptococci serologically was developed.[5] According to this system, hemolytic streptococci and some nonhemolytic streptococci may be primarily subdivided into twelve groups. Members of each group elaborate a somatic carbohydrate designated C, which is serologically recognizable with suitable sera. Nonhemolytic or viridans streptococci are included in categories other than groups, because they form no demonstrable C substance, they cannot be grouped serologically. They are, however, sometimes subject to type classification.[6]

Twelve groups designated by letters A to N (with I and J omitted) have been recognized, and several have peculiar habitats where they usually reside, although they occasionally occur elsewhere. In some instances, e.g. strangles in horses, the streptococci involved are uniquely pathogenic, in other cases, one group is chiefly responsible for a certain disease, as illustrated by mastitis in cattle, which is usually caused by group B, although members of groups A and C may occasionally induce this disease. Members of several groups are sometimes encountered in the carrier state in unusual environments, where they even occasionally act as true pathogens. Therefore the mere recovery of a streptococcus in a given environment does not necessarily prove that it is inducing a disease, other data may be necessary, indeed they usually are.

GROUP A STREPTOCOCCAL INFECTIONS

In man about 95 per cent of streptococcal diseases are caused by members of group A, and the remainder by members of other groups and of the viridans streptococci. Group A streptococci are further divisible into serologic types, the significance of which is discussed later, but no type has been shown to be responsible for any one disease. Indeed, the many clinical manifestations of human streptococcal infections are caused by many different types.

Relation to Rheumatic Fever. So far only group A streptococci have been shown to induce the precursory infections that are followed by rheumatic fever. From the peculiar chain of events (precursory streptococcal infection, phase 1, a latent period, phase 2, and then the rheumatic fever, phase 3), it appears that the rheumatic fever is not a complication in the ordinary sense of the word, but a sequel of the streptococcal infection.

This picture is particularly well demonstrated in epidemic form occurring in milk-borne outbreaks of sore throat, such as those reported by Madsen and Kalbak,[7] where the peak of some streptococcal epidemics preceded the first case of rheumatic fever by over two weeks, and the epidemics had entirely subsided before the majority of the cases of rheumatic sequelae appeared. In military establishments such as barracks a similar sequence of events is frequently observed[8], during World War II, many group A streptococcal epidemics were carefully studied with modern serologic technics, and it was well proven that no other infections, either respiratory or nonrespiratory, acted as forerunners of rheumatic fever.[9, 10, 11, 12] This negative evidence is almost as important as the positive. Moreover, it has been established in schools and hospitals that group A streptococcal infections are particularly dangerous among subjects who have previously had rheumatic fever, for among such subjects the incidence of rheumatic recurrences is much higher than in individuals who have not previously had this disease.

Familial Susceptibility. Family epidemics of streptococcal infection, such as those studied by Paul and Salinger,[13] illustrate well various clinical entities induced probably by single strains of streptococci, for under home conditions where special precautions are not taken, streptococcal infections travel through a family with great rapidity. This brings up the peculiar human beings among whom rheumatic fever thrives. Several observations record the existence of this disease in many members of a family, and there is quite suggestive statistical evidence[14] that there is probably an inherited susceptibility to rheumatic fever, but it is often difficult to rule out the concomitant influence of streptococcal microenvironment. Indeed, because in many instances, particularly among troops, there has been little definite proof of a family susceptibility, this question is as yet in a state of flux.

Effect of Prophylaxis on Incidence of Rheumatic Fever. Many careful studies have definitely shown that if the precursory streptococcal infection is prevented by the sulfonamides[15] or penicillin, and sometimes if it is cut short by penicillin treatment very early in the course of streptococcal sore throat, then rheumatic sequelae do not occur.[16] Moreover, in the presence of an epidemic induced by sulfa-resistant strains of streptococci, rheumatic fever sequelae occur even though the patients take large amounts of the respective sulfa drugs, therefore it must be concluded that when

these drugs are prophylactically effective, they act upon the streptococcal element and not upon the rheumatic fever. These observations have both practical and theoretic significance, for by a process of elimination they confirm the validity of the thesis that a disease induced by group A streptococci plays an important and necessary role in the causation of rheumatic fever.

Cardiac Lesions as Sequelae. The cardiac manifestations of rheumatic fever are obviously more serious than the arthritic, and in recent years even though the total incidence of rheumatic fever is apparently diminishing the incidence of polyarthritis rheumatica is apparently falling more rapidly than is that of carditis. Therefore a careful study of possible cardiac involvement after streptococcal infections is even more important than in former years.

The well demonstrated cause and effect relationship between a streptococcal forerunner and rheumatic carditis makes it highly desirable to study carefully all patients following infection with group A streptococci in an attempt to learn whether this serious sequel has or has not occurred. The diagnostic significance of polyarthritis is unquestionable, but the heart may be involved in the absence of arthritis or chorea. The most definite evidence of such involvement is stethoscopic and electrocardiographic, but obviously it is impractical to have semiweekly electrocardiograms on all patients for two to five weeks following streptococcal respiratory infections. However, determination of the erythrocytic sedimentation rate every seven to ten days for four to five weeks following such infections, and further clinical and laboratory examination of those patients whose erythrocytic sedimentation rate remains abnormal or who have rising rates after a period of normality, would permit the detection of many instances of carditis that are now overlooked.

In view of the widely recognized relationship between streptococcal upper respiratory infection and rheumatic fever, the observations of Levy and his coworkers[17] are of extreme interest. In a collaborative investigation in five different cities during World War II, among 4131 draftees rejected from military service, 60 per cent were found to have had rheumatic cardiac valvular disease, but among 2205 of the latter from Boston, Chicago, New York, and Philadelphia, 69 per cent denied having had rheumatic arthritis or chorea. As their unrecognized earlier rheumatic fever occurred in a period when rheumatic polyarthritis was relatively much more frequent than it is today, it seems safe to assume an even greater current relative incidence of early rheumatic carditis below the clinical horizon following group A streptococcal infections. Moreover, as there are now available better techniques than formerly for recognizing these cases of rheumatic carditis d'emblée, it behooves the medical profession to apply these techniques in an effort to arrest or retard the progressive downward course of rheumatic heart disease. The protection of the patient with slight rheumatic carditis from additional group A streptococcal infections is a logical measure not attended with insurmountable difficulties, and one that should challenge both practicing physicians and public health authorities.

DIAGNOSTIC SIGNIFICANCE OF SERUM COMPONENTS

A streptococcal infection preliminary to rheumatic fever may be so mild as to have been easily overlooked without carefully repeated nose and throat

cultures Moreover, because a quarter to a third of patients at the time of the onset of their rheumatic fever have lost the group A streptococci from their nose and throat, other evidence of the occurrence of the precursory streptococcal infection is requisite. This has been furnished by demonstrating antibodies to various components of group A streptococci in these patients' sera.

Such antibodies are of two general classes: (*a*) those against the extracellular antigens elaborated by streptococci into culture media or into the tissues surrounding streptococcal lesions, (*b*) those against somatic antigens of the streptococci.

Antibodies against Extracellular Antigens In Table 1 are summarized the various extracellular antigens that have been so far identified, their antibodies and, schematically, *the relative frequency with which these* antibodies have been encountered in patients with streptococcal infections without, and with, rheumatic fever sequelae. Other extracellular antigens probably exist.

Table 1. Antibodies against Extracellular Antigens Elaborated by Group A Streptococci

EXTRACELLULAR ANTIGENS	ANTIBODIES	RELATIVE ANTIBODY PRODUCTION IN HUMAN INFECTIONS	
		No RF	RF
Streptolysin O	Antistreptolysin O	++	+++
Streptolysin S	Antistreptolysin S	++	+
Streptokinase (Fibrinolysin)	Antistreptokinase	++	+++
Hyaluronidase (Types 4 & 24) ("precursor"?)* all types	Antihyaluronidase	++±	++++
Proteinase	Antiproteinase	(+)?	(+±)?
Desoxyribonuclease (Dornase)†	AntiDORNase†	+	++
Ribonuclease	Antiribonuclease	?	?

ANTISTREPTOLYSIN O Antistreptolysin O[18] has been most widely studied in this connection, and for a decade numerous reports have indicated that rheumatic fever patients develop abnormal concentrations of these antibodies with greater frequency and in higher concentrations than do patients infected with streptococci who do not develop rheumatic fever.* There was however, little information concerning the relative capacity of the various infecting strains to form streptolysin O. This lack of information has been overcome in a study by Anderson, Kunkel, and McCarty,[19] who employed sera from patients in an epidemic where three types of streptococci were inducing most of the infections, hence the antigenic stimuli were similar. There were five groups of patients I, those in which one streptococcal type was active, II, those probably infected with more than one type, III, those

frequently observed.

effectively treated with penicillin, IV, those not effectively treated with penicillin, and V, those who developed rheumatic fever It was found that the rheumatic fever group developed on the average by far the highest concentration of antistreptolysin O, while those in whom penicillin therapy was effective developed the least.

ANTISTREPTOKINASE A similar general tendency existed when the same

streptolysin O formation.

That the study of two different antibodies demonstrates a higher incidence of streptococcal infections than does testing for only one antibody is shown in Figure 1 summarized from these authors' data Such a summary indi-

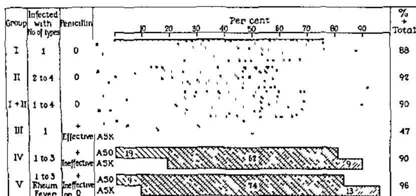


Fig 1 Antistreptolysin O and antistreptokinase production by different patients infected with the same types of group A streptococci

cates the hazard of denying the existence of a streptococcal infection on the basis of absence of any one antibody The chart also illustrates graphically the most marked average production of both of these antibodies by the patients who developed rheumatic fever

The gamma globulin content of these patients' sera at various times following their streptococcal infections was again most marked in the rheumatic fever group Other noteworthy phenomena were observed. Group III, effectively treated with penicillin, had an early rise in gamma globulin which then temporarily remained almost level and finally fell off in four to six weeks Even more interesting was the occurrence in the sera of the rheumatic group of a higher average gamma globulin at the onset of their nasopharyngitis than was present in the nonrheumatic group This was attributable, in part, to abnormal concentrations of antistreptolysin O in the sera of most of the rheumatic subjects at the onset of their latest streptococcal infection

Table 1 indicates the existence of at least seven extracellular antigens of group A streptococci and, in patients' sera, the possible occurrence of corresponding antibodies against them. It seems reasonable to assume that the marked formation of gamma globulin by rheumatic patients is prob-

ably an index of intense production, by these patients, of antibodies other than the two just discussed Indeed, observations of Quinn,[20] of Harris, Harris and Nagel,[21] and others indicate that a distinctly higher concentration of antihyaluronidase occurred among their rheumatic fever patients than among other patients infected with group A streptococci who did not develop rheumatic fever, and some of these observers feel that a high antihyaluronidase content in a patient's serum is a better indicator of a probable rheumatic fever than is furnished by titration of its antistreptolysin O content But let it be noted that no single serologic test yet devised is diagnostic of rheumatic fever All have only presumptive significance when considered along with other evidence

ANTIHYALURONIDASE The hyaluronidase and antihyaluronidase question has elicited much discussion with respect to the pathogenesis of rheumatic fever The observations[22] that hyaluronic acid constitutes most of the capsular substance formed by groups A and C streptococci and also some of the interfibrillar material of collagen, suggested that a possible causal connection exists between lesions of collagen and an action of hyaluronidase which in vitro attacks this viscid polysaccharide. This hypothesis was supported by the demonstration that substances containing hyaluronidase, for example extracts of bovine testes or of certain bacteria, act as spreading factors[23] when injected intracutaneously into various animals Several bacterial hyaluronidases induce animals to produce the antihyaluronidase which combines specifically with the hyaluronidase derived from its respective specific source, and not from others Thus although the hyaluronic acid substrate is common to all, each enzyme has serologic specificity.

Although in employing the mucin clot prevention test technique Crowley[24] showed that only types 4 and 22 of group A streptococci elaborate easily detectable extracellular hyaluronidase, Pike,[25] by employing the turbidity reduction technique and streptococcal hyaluronic acid as a substrate, found hyaluronidase to be elaborated by over half of the noncapsular group A streptococci tested and also by some capsulated strains On the other hand, the demonstration that the majority of patients undergoing group A streptococcal infections elaborate antihyaluronidase into their sera strongly suggests that in most group A streptococci, the antigen hyaluronidase probably exists as a precursory substance not as yet always directly demonstrable in vitro. Moreover, the formation by so many patients of antihyaluronidase suggests that this enzyme, probably in the form of a precursor, is an exceptionally strong antigen The elaboration by rheumatic fever patients, compared with nonrheumatics, of relatively larger amounts of antihyaluronidase is probably an example of their marked tendency as a group to form relatively large amounts of antibodies against various components of streptococci

Hypothetically it would seem that if bacterial hyaluronidase were responsible for widespread injury of collagen distant from the focal bacterial lesion, then those microorganisms producing the largest amounts of this enzyme would be the most potent inducers of rheumatic fever; but this is contrary to observed phenomena At least two epidemics have been studied which were caused by type 4 group A streptococci among convalescents from rheumatic fever without being followed by rheumatic recurrences Human group C streptococcal infections, moreover, have not been observed to induce rheumatic fever even in rheumatic subjects, although this group

of streptococci quite frequently form enough hyaluronidase to be easily demonstrable in vitro, and pneumococci and clostridia, also potent producers of hyaluronidase, are conspicuously negative as causative agents of infections that are forerunners of rheumatic fever. Until more light is thrown on this subject, therefore, it seems well to assume that intense antihyaluronidase production by rheumatic fever patients is a concomitant, rather than a causal, phenomena with respect to rheumatic fever.

OTHER EXTRACELLULAR ANTIGENS The other extracellular antigens and their antibodies listed in Table 1 have been much less studied with respect to rheumatic fever, but it has been definitely established that these antibodies are often formed during or following streptococcal infections.[26] The use of streptokinase and streptodornase to dissolve fibrinous exudates has very useful therapeutic potentialities.[27] The relatively lower antistreptolysin S formation by rheumatic fever patients during a rheumatic attack and the tendency for them to form larger amounts with recovery[28] deserve further study that will doubtless be facilitated by Bernheimer's[29] determination of improved methods for preparing this antigen.

Table 2 Antibodies against Somatic Antigens of Group A Streptococci

SOMATIC ANTIGENS	ANTIBODIES	SPECIFICITY
C Carbohydrate	Anti-C precipitins	Group specific
Nucleoproteins	Antinucleoproteins	Common to many cocci
T Proteins	Anti-T agglutinins	Some type-specific; some common to several types
M Proteins		Type-specific
	Protective	in vivo
(over 40 types)	Bacteriostatic	in vitro
	Anti-M precipitins	in vitro*
	Anti-M agglutinins	in vitro*

* With properly absorbed sera

Antibodies against Somatic Antigens Patients suffering from group A streptococcal infections elaborate antibodies also against the somatic antigens of streptococci. While this question has received only little attention, investigations, carried out mainly in our laboratories, have indicated its usefulness in suggesting a possible mechanism in the induction of rheumatic fever. [illegible]

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serologic type of group A streptococci that is infecting a patient, are those that react with the streptococcal M proteins. Such type-specific antibodies have protective import both in active and passive immunity, they are bacteriostatic in human sera, and under proper conditions positive precipitin reactions indicate the existence of type specific antibody. The difficulties often encountered in testing patients' sera for anti-M precipitins probably stem from our inability as yet to prepare pure M extracts unmixed with other somatic antigenic components. There are over forty serologic types among the group A streptococci, and each produces its own specific M antigen.

DEMONSTRATION OF TYPE-SPECIFIC ANTIBODIES While the type or types of

group A streptococci that are infecting a patient may be readily determined by precipitin tests applied to the strains recovered from him, the bacteriostatic test is the only reliable technique so far developed for demonstrating strictly type-specific antibodies in his serum Two methods of measuring bacteriostatic antibodies have been employed, the direct and the indirect In the former,[30] patients' heparinized blood is incubated with suitable dilutions of the bacteria, then the mixture is inoculated on blood agar and incubated to determine how much bacterial growth has been inhibited This test must be done within a few hours after the patient's blood is obtained, hence, accurate comparative measurements of this antibody over considerable periods are not feasible With the indirect technique,[31] the sera can be refrigerated, and several, previously obtained at different times from a patient, may be tested simultaneously for their respective bacteriostatic antibody content. Dilutions of these sera, heparinized blood from a healthy child, and dilutions of streptococci are mixed and incubated, then plated on blood agar and again incubated When suitably controlled, inhibition of growth indicates existence of type-specific antibody; by employing suitable dilutions of serum and streptococci this test is roughly quantitative

CLINICAL STUDY: DEVELOPMENT OF ANTIBODIES IN A SERIES OF PATIENTS

Table 3 summarizes the relative development at weekly intervals of antibodies against two extracellular antigens and two somatic antigens by

Table 3 Comparative Formation of Antibodies against Group A Streptococcal Extracellular and Somatic Antigens by the Same Group of Patients

NATURE OF GROUP A STREPTOCOCCAL INFECTION	UNCOMPLICATED	COMPLICATED	WITH RHEUMATIC FEVER SEQUELAE*	TOTAL
ANTIBODIES AGAINST EXTRACELLULAR ANTIGENS.				
Antistreptolysin O increase, %	69.7	75.0	85.3	77.1
Average beginning of rise, weeks	2.4	2.3	2.0	2.4
Antifibrinolysin increase, %	62.9	80.0	80.9	73.0
Average beginning of rise, weeks	3.1	2.5	2.3	2.6
ANTIBODIES AGAINST SOMATIC ANTIGENS				
Bacteriostatic antibody increase, %	66.7	68.8	87.9	75.6
Average beginning of rise, weeks	4.2	3.9	6.1	5.1
Range, weeks	2–10	2–8	1–13	
Precipitin reactions with M extracts:				
Homologous type, %	45.5	56.2	85.3	63.9
Heterologous type, %	33.3	43.8	61.8	46.9
Average beginning of rise, weeks	3.6	2.6	6.0	4.8
Range, weeks	1–8	1–5	1–23	

* Twelve per cent of rheumatic patients also had purulent complications

a fairly large group of our patients infected with group A streptococci.[32] They were divided into three subgroups· (a) those without complications or sequelae, (b) those with purulent complications, and (c) those with rheumatic fever sequelae, of whom four also had purulent complications. We were unable to measure a possible antifibrinolysin increase in some of

these patients' sera because they contained high concentrations of this antibody at the onset of the latest streptococcal infections, but it was possible to compare the development of the other three antibodies. The rheumatic fever group developed on the average relatively more antibodies than did the nonrheumatic group when tested with these four different antigens Although the measurable antibody increase against the extracellular antigens appeared at about the same average time following infection in all groups of patients, there was an average delay of approximately two to three weeks in the appearance of antibodies against the somatic antigens among the rheumatic fever group as compared with the nonrheumatic, this was illustrated in both the bacteriostatic and anti-M precipitin tests, and confirm some earlier observations with the anti-M precipitin technique [33, 34] The possible significance of this delay in the pathogenesis of rheumatic fever is not as yet explained.

Figure 2, summarizing graphically the comparative antibody production by the same group of our patients, indicates again that the more tests one

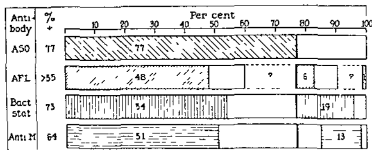


Fig 2 Distribution of four different antibodies in eighty-three patients infected with group A streptococci

applies to the same samples of sera, the more convincing is the evidence of a previous recent streptococcal infection Among patients undergoing

abnormal concentrations of antistreptolysin O reacted negatively with one or more of the other antigens The application of four tests, however, demonstrated antibody formation against one or more streptococcal antigenic components in all instances

A detailed analysis was made of the entire series of patients in whom it was possible to initiate these investigations very near the time of onset of their streptococcal infections and to continue them through the period when rheumatic sequelae were apt to occur, and for several months and sometimes for two or three years when these sequelae occurred The analysis showed the following:

1. At the onset of an infection with a given type of group A streptococci, a patient's serum contained no bacteriostatic antibodies against that

type, although it often contained abnormal amounts of antistreptolysin O or antifibrinolysin, and sometimes of bacteriostatic antibodies against streptococci belonging to types heterologous to that recently infecting the patient

2 Type specific bacteriostatic antibodies usually appeared later in the course of infection or with recovery, and at times persisted for months or years though occasionally they were demonstrable for only a few months, they were probably an index of type specific immunity.

3 Bacteriostatic antibodies against heterologous types found very early in an infection probably indicate previous infections with streptococci belonging to those respective types.

COMMENT

It now seems probable, from data derived with several different investigative techniques, that many, possibly most, persons living in this general geographic area suffer one or more group A hemolytic streptococcal infections during their lifetime This is indicated by direct clinical and bacteriologic studies, and also in the general population by the gradual development of antibodies against the streptococcal erythrogenic toxins and the development of antistreptolysin O, and particularly by the recent studies of antihyaluronidase in sera by Friou and Wenner,[35] Quinn,[36] and Harris and Harris [37] These authors reported the blood of newborn infants to contain practically the same amount of this antibody as that of their mothers, with a marked diminution for two to three years followed by a gradual average rise in mean titer until early adulthood While this is possibly an example of "physiologic antibody formation," it seems more logical to conclude that the rise in antihyaluronidase throughout childhood and youth is due to repeated group A streptococcal infections, because these antibodies have been demonstrated with the tests that have been made with hyaluronidase obtained from group A streptococci, and not with hyaluronidase from other sources

As stressed by Powers[38] and his collaborators, early in life group A streptococcal infections are often diffuse and so noncharacteristic that their etiology requires bacteriologic and serologic demonstration However, with

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cocci heterologous in type to those previously active in any given patient The frequency of repeated upper respiratory infections which are probably caused by streptococc ... to the development of their ... the studies of rheuma... tions of the "prerheumatic child" correspond closely with those of "streptococcosis" (Powers) in young children

For the time being we may postulate that there is a tendency (possibly inherited) in the tissues of certain persons to overreact to these streptococcal infections with the development of manifestations recognized as rheumatic fever, and that this tendency is brought out and increased by the repeated streptococcal infections they suffer The average higher antibody formation against various streptococcal products, the average greater cutaneous hypersensitivity to streptococcal extracts,[2, 39, 40] and the delayed, tuberculin type of hyperreactivity of rheumatic patients to intravenous

injections of streptococcal extracts[40] all appear to be examples of their hyperresponse to streptococcal antigens If this theory is correct, we may furthermore regard each rheumatic occurrence as due to a group A streptococcal infection with a serologic type of streptococcus that probably had not infected the patient previously Then each recurrence of rheumatic fever is indeed a new attack of this disease occurring in tissues that have been reconditioned by previous streptococcal infections, and is not a relapse of a latent infection such as occurs in syphilis

ANIMAL STUDIES

During many years work in experimental infections of rabbits with streptococci, we have demonstrated that two types of reactivity can be induced with minute inocula of lowly virulent strains, according to the route of inoculation, namely, hyperreactivity from focal infections,[41] and immune hyporeactivity from intravenous immunization[42] It was also found that rabbits immunized with viridans streptococci often develop tissue hyperreactivity to subsequent infection with a strain of group A or group C streptococci, but hyporeactivity to the immunizing viridans strain[43, 44] Later, when the significance of human infections with different *types* of streptococci was appreciated, we showed[15] that prolonged immunization or repeated infections of rabbits with one serologic type of group A streptococci usually caused the animals' cutaneous tissues to respond to subsequent inoculation with immune hyporeactivity to inoculation with the homologous type strain, quite frequently the same rabbits showed hyperreactivity to inoculation with heterologous type strains

CONCLUSION

From both bedside studies and animal experimentation the hypothesis is presented that the successive group A streptococcal infections suffered by many patients lead to a heightened irritability of their tissues to subsequent infections with group A streptococci heterologous in type to those with which they had previously been infected; and that when this heightened reactivity reaches a certain degree it may manifest itself as rheumatic fever

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DISCUSSION

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During the years that have elapsed since 1931, when Dr Alvin Coburn's monograph on the subject appeared, there has accumulated overwhelming evidence that the hemolytic streptococcus is the precipitating agent of nearly all, if not all, attacks of rheumatic fever.

In spite of the considerable data that have been collected in regard to the streptococcal hypothesis, there is still lack of information regarding the role of this organism in the continuation of rheumatic fever. It is my personal opinion that once an attack of this disease has been initiated by the streptococcus, it may in some instances continue in its active state for many months without the incrimination of further streptococcal activity The mechanism by which the rheumatic process is kept going still needs to be explained.

Dr. Swift has emphasized the importance of good bacteriologic data in determining whether hemolytic streptococci isolated from the upper respiratory passages are organisms which have been carried for some time and therefore relatively inconsequential, or whether they are fresh invaders and hence the cause of a new infection I should like to reemphasize his statements and especially point out the value of good baseline throat culture data in the evaluation of respiratory infections.

The work which has been done at the Rockefeller Hospital on type spe-

cific bacteriostatic antibodies is extremely important and adds a new and significant immunologic tool to those we already have for determining the streptococcal experience of patients

My final comment in regard to Dr. Swift's paper is concerned with his remark that antibiotics are not effective in preventing rheumatic fever once a streptococcal infection becomes well established. The interpretation of this statement depends perhaps upon what is meant by well established In this connection it is of interest to point out that in definite rheumatic subjects at the House of the Good Samaritan approximately twenty to twenty-five authentic clinical hemolytic streptococcus infections treated within a period of twenty-four hours of onset and for a period of ten days have not been followed by rheumatic fever recurrences in a single instance. During this same period among a small number of controls we have observed several rheumatic fever recurrences Of course, the number of patients involved is still too small to be sure whether or not these observations are significant

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OBSERVATIONS REGARDING ARTIFICIALLY INDUCED SUBCUTANEOUS NODULES IN RHEUMATIC FEVER PATIENTS*

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Although subcutaneous nodules were recognized as an important manifestation of rheumatic fever even before 1881 when Barlow and Warner[1] published the first comprehensive clinical description of these structures, the mechanism by which they are produced is still poorly understood In 1935 at the House of the Good Samaritan studies aimed at elucidating possible factors involved in the development of subcutaneous nodules resulted in the first successful induction of the structures by artificial methods[2]

Nodules were at first artificially induced on the elbows of patients suffering from active rheumatic fever by injecting 2 to 3 cc of the patient's own blood subcutaneously over the olecranon process and then applying daily frictional pressure to this area for a period of ten days. Later it was [illegible]

the development of nodules

From the data collected in these preliminary studies it appeared that the frequency with which nodules could be successfully induced and the size of the induced lesions were related roughly to the degree of activity of the rheumatic fever process The microscopic architecture as well as the clinical characteristics of the induced nodule seems to be essentially the same as that of subcutaneous nodules which spontaneously appear in

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the course of active rheumatic fever. In both kinds of lesions the histopathologic picture depended somewhat upon the age of the structures[3]

Subcutaneous nodules appear spontaneously in the course of rheumatic fever, rheumatoid arthritis, and even occasionally in disseminated lupus erythematosus Although the nodules of rheumatic fever and rheumatoid arthritis may in some instances be distinguishable by their histopathology,[4] they are in many respects quite similar and in general they seem to be specific for the "collagen" diseases Of still greater significance is the fact that the microscopic architecture of the subcutaneous nodule of rheumatic fever is very similar to that of the myocardial lesions in this disease Furthermore, most rheumatic fever patients who develop subcutaneous nodules also develop definite clinical evidence of valvular heart damage It is logical to conclude that the pathologic mechanism involved in the production of subcutaneous nodules is very similar to that involved in the production of rheumatic heart disease

The demonstration that it was possible artificially to induce subcutaneous nodules essentially identical with those developing spontaneously seemed to offer a method of studying one of the basic processes of rheumatic fever During the years which have elapsed since our original report,[2] we have continued to make observations aimed at elucidating the mechanism involved in the development of subcutaneous nodules These observations form the basis of the present report

METHODS

A number of different methods have been used for inducing nodules and for control purposes The procedure used in an attempt to induce a nodule is sometimes referred to as a nodule test, but, in using this terminology, it is not our intention to propose the procedure as a clinical test for rheumatic fever

The standard procedure consisted in infiltrating the region of the olecranon process of one elbow with 1 cc or less of 1 per cent procaine, using for this purpose a small syringe and a fine (No 26) needle After a few minutes, using another syringe, and a larger needle (usually No 20, occasionally No 21 or No. 22), blood was removed under sterile precautions from the antecubital vein of the opposite arm and immediately injected subcutaneously in the anesthetized area In the earlier tests 2 to 3 cc. of blood was usually used, but later the amount was increased slightly to about 3 to 4 cc The needle used for injecting the blood was inserted through the puncture hole in the skin previously made by the procaine needle, and, as the blood was injected, the needle was redirected several times so that the blood could be forced into the deep tissues overlying the bone as well as into the looser subcutaneous tissues Other tests were performed with the same standard procedure using the anterior aspect of the knee and other sites

In some tests blood from patients suffering from severe rheumatic fever and blood from healthy young adults was injected into the elbows of other patients, most of whom had recently recovered or had nearly recovered from rheumatic fever In these cross tests, as soon as the blood was obtained from the donor, it was transferred to a vial containing a small amount of sodium citrate in order to prevent clotting The citrated blood was always used within a period of one hour from the time it was obtained.

Another method consisted in using the patient's own blood, but in contrast to the standard traumatizing technique, the blood was injected slowly into the subcutaneous tissues through a fine needle so as to produce as little trauma as possible. In other tests the standard traumatizing technique was used but sterile saline was substituted for blood

Finally, in studies which are not yet completed and which will be reported only briefly in the present communication, tests have been performed with hyaluronidase This substance has been injected subcutaneously through a fine needle (No 26) and without previous anesthetization of the skin in amounts up to 30 turbidity reducing units contained in a total volume of only 0 5 cc of normal saline

The injection of small amounts of 1 per cent procaine alone had previously been found to be an ineffective method of inducing nodules[2] and, therefore, further control tests with this material have not been done

CLINICAL MATERIAL

The present report is based upon all of our observations to date and includes the original data used for our previous communications,[2, 3] as well as the material collected since then

A total of 892 different tests have been performed on 362 rheumatic fever subjects The patients varied from four to twenty-two years of age and averaged 10 6 years Approximately 95 per cent of the patients were between four and sixteen years of age In some instances for purposes of comparison two or more tests were done simultaneously but at different sites in the same patient, in other instances a particular patient was tested at different times over a period of several months or years at various stages of his disease

The rheumatic fever patients tested have been divided into the following four groups according to the activity of the disease at the time the tests were performed (1) those with O activity—patients who apparently had recently recovered from a definite attack of rheumatic fever and who were still convalescing on the wards of the hospital, (2) those with + activity—patients ill with low grade rheumatic fever which in most instances was manifested only by consistent elevation of the erythrocyte sedimentation rate, (3) those with ++ activity—patients with moderately active disease presenting clinical as well as laboratory evidence of rheumatic fever, and (4) those with +++ activity—patients with severe rheumatic fever and carditis

All of the patients in the last category presented obvious signs of valvular heart damage, and a little less than half of them had congestive heart failure at the time the tests were performed About two-thirds of the patients in the first three groups had valvular involvement while the remaining rheumatic patients had no signs of heart damage In accordance with the classification of the American Heart Association[5] the diagnosis of rheumatic heart disease (RHD) has been used for those individuals with valvular damage and potential rheumatic heart disease (PRHD) for those rheumatic patients without signs of cardiac involvement

Forty-eight standard olecranon tests were performed in patients who at the time presented chorea as at least one of their manifestations of rheumatic fever

In addition to the rheumatic fever subjects, 158 other individuals served as controls They consisted of seventy-nine feebleminded children, thirty

children with bone tuberculosis, sixty patients in the first or second week of scarlet fever, four patients with subacute bacterial endocarditis, two patients with disseminated lupus erythematosus, and thirteen patients with various other conditions unrelated to rheumatic fever. Except for one of the patients with disseminated lupus erythematosus who was tested four different times during the course of a prolonged illness, each of the other non-rheumatic fever patients was tested only once in the region of the olecranon process and with the standard technique. The controls varied from three to twenty years of age and averaged 9.2 years. About 95 per cent of them were between four and sixteen years of age

RESULTS

Development of Induced Nodules When blood was used for the test, a hematoma was produced at the site of the injection In some persons the discoloration and diffuse subcutaneous thickening which were always present gradually subsided and the tissues regained their normal appearance and texture by the end of one to two weeks. In others, as the discolored

*Table 4. Frequency of Induced Nodules in Relation to Rheumatic Fever Activity**

DEGREE OF RHEUMATIC FEVER ACTIVITY	NUMBER OF TESTS	SUCCESSFULLY INDUCED NODULES	
		Number	Per cent
0 (Quiescent)	165	25	15 2
+ (Mild, usually subclinical)	139	66	47.5
++ (Moderate)	91	65	71 4
+++ (Severe)	56	48	85 7
TOTAL TESTS	451	204	45 2

* This analysis is confined to tests performed with the standard technique and in the region of the olecranon process.

swelling subsided there appeared, usually by the end of the first or during the second week, a moveable, subcutaneous nodulelike structure In the beginning this was poorly defined and somewhat soft, but usually within another week or more it became definitely circumscribed and firm The size varied from about 2 to 10 mm in diameter Clinically, these induced nodules, which were usually visible as well as palpable, could not be distinguished from the subcutaneous nodules which appear spontaneously in patients with rheumatic fever.

In a relatively few instances, tests over the tip of the elbow were followed by the development of a rather large, soft, painless swelling of the olecranon bursa and, in such cases, the presence of one or more firm nodules could usually be palpated within the soft swelling

Frequency, Size, and Duration of Nodules Induced by the Standard Technique over the Olecranon Process of Rheumatic Fever Patients The standard test involving the injection of the patient's own blood subcutaneously over the olecranon process of the elbow was performed 451 times in 340 rheumatic fever patients In Table 4 the frequency with which nodules were successfully induced by these tests is related to the activity of the rheumatic process at the time the tests were performed, while in Table 5

the size of the induced nodules, which were graded from + to +++, is related to rheumatic activity.

From these data it is evident that there is a strong correlation of both frequency and size of the nodules with the severity of the illness In patients who although still hospitalized apparently had recovered from recent rheumatic fever the incidence of induced nodules was about 15 per cent and those nodules which could be induced were quite small in every instance but one In those patients who obviously were suffering from severe rheumatic fever, the standard technique induced nodules in about 86 per cent, and well over half of the structures were of moderate (++) or large (+++) size

Once a nodule had made its appearance, it remained for as short a time as a week to as long a time as well over a year Nodules remaining readily detectable for periods of two to six months were not uncommon A detailed analysis of the duration of the induced nodules has not been made, but inspection of the data reveals certain apparent correlations, namely, that

*Table 5 Size of Induced Nodules in Relation to Rheumatic Fever Activity**

DEGREE OF RHEUMATIC FEVER ACTIVITY	NUMBER OF INDUCED NODULES	DISTRIBUTION OF NODULES BY SIZE			Total ++ and +++	
		+	++	+++	Number	Per cent of total
0 (Quiescent)	25	24	1	0	1	4
+ (Mild, usually subclinical)	66	49	9	8	17	25 8
++ (Moderate)	65	32	20	13	33	50 8
+++ (Severe)	48	19	20	9	29	60 4
TOTAL	204	124	50	30	80	39 2

* This analysis is confined to tests performed with the standard technique and in the region of the olecranon process

the more active the rheumatic process at the time of the test and the bigger the size of the nodule, the longer the structure seemed to remain palpable

The duration of the active rheumatic process also seemed to be a factor which influenced the duration of the induced nodules In the group of patients whose rheumatic fever activity had subsided at the time the tests were done nearly all of the induced nodules were small, most of them disappeared again within one to two weeks, only a very few persisted for periods of one to two months, and none lasted longer than two months On the other hand, in those patients who had active rheumatic fever at the time of the test, and especially in those who presented clinical as well as laboratory manifestations of disease, nodules were on the average larger and often continued to be present for many months. Even small (+) nodules in the clinically active patients whose illness was chronic persisted for as long as two to four months in contrast to their short duration in the inactive group

In general then the duration of nodules showed a rough correlation with the size of the induced structures, the degree of rheumatic fever activity at the time of the test, and the duration of the rheumatic process.

It is of interest that in many instances when spontaneous and induced

nodules were both present, they often began to get smaller at about the same time and disappeared within a few weeks of each other However, this interesting parallelism was not constantly observed.

Results of the Standard Olecranon Tests in Control Subjects Further evidence of the relative specificity of the induced nodule reaction for rheumatic activity is furnished by the results of 191 standard olecranon tests in 188 control subjects. The data are presented in Table 6 In this group induced nodules were obtained in seven instances and all of these structures were of small (+) size

One induced nodule occurred among thirty patients with bone tuberculosis It was biopsied and examined by Dr. Granville A. Bennett who

Table 6 Results of Standard Nodule Tests in the Olecranon Region of Control Subjects

SOURCE OF CONTROLS	NUMBER OF INDIVIDUALS	NUMBER OF TESTS	NUMBER OF INDUCED NODULES
Feebleminded children	79*	79*	1*
Patients with bone tuberculosis	30	30	1
Patients with scarlet fever	60	60	4
Patients with subacute bacterial endocarditis	4	4	0
Patients with disseminated lupus erythematosus	2	5	1
Patients with miscellaneous diseases unrelated to rheumatic fever	13	13	0
TOTAL CASES EXCLUSIVE OF RHEUMATIC FEVER PATIENT AND PATIENTS WITH DISSEMINATED LUPUS ERYTHEMATOSUS	185	185	5 (2 7%)

* The feebleminded child in whom an induced nodule developed had had rheumatic fever six months previously and was found to have rheumatic heart disease with involvement of the aortic and mitral valves

described it as being "fibrous tissue, almost completely devoid of inflammatory changes, but containing a small irregular cavity which is filled with blood cells" The material did not seem to him to be characteristic of a rheumatic nodule

Four of the nodules occurred in scarlet fever patients and two of these structures were also studied microscopically by Dr. Bennett. His impression was that one was not especially suggestive of rheumatic nodule and that the other was a subcutaneous nodule "more like those seen in rheumatoid arthritis than those in rheumatic fever"

The sixth induced nodule among the controls developed in a ten-year-old girl who was found at autopsy to have had a chronic inflammatory polyserositis of the type seen in disseminated lupus erythematosis Two previous and one subsequent test in the same patient and one test in another patient who was believed to have the same disease failed to produce nodules The successfully induced nodule resulted from a test performed during the third week of a severe recrudescence of the disease process and at a period when the patient was having joint pains and pericarditis It was of moderate size and although subsequently it became smaller, it persisted and could still be detected at the time of the patient's death nine months later. Clinically it was indistinguishable from nodules that have

been induced in rheumatic fever patients Unfortunately, the specimen obtained at autopsy for microscopic examination was not satisfactory and the single section that was made showed an "irregular cavity in the fibrous tissue with large numbers of mononuclear cells around its periphery" It was not believed by Dr Bennett to resemble a rheumatoid nodule or a nodule of rheumatic fever Because of the possible relationship of disseminated lupus erythematosus to rheumatic fever and because of the occasional observation of spontaneous nodules in disseminated lupus erythematosus, it is not surprising that a nodule could be induced in this patient

The facts related to the induction of the seventh nodule in the control group are of especial interest The nodule occurred in one of seventy-nine feebleminded children It was a small but definite round circumscribed

Table 7 Relation of Heart Status to Frequency and Size of Induced Nodules

DEGREE OF RHEUMATIC FEVER ACTIVITY*	HEART STATUS	NUMBER OF TESTS	INDUCED NODULES		SIZE OF NODULES		
			Number	Per cent	+	++	+++
0	With heart disease (RHD)	100	15	15	14	1	0
	Without heart disease (PRHD)	65	10	15.4	10	0	0
+	With heart disease (RHD)	102	54	52.9	38	9	7
	Without heart disease (PRHD)	37	12	32.4	11	0	1
++	With heart disease (RHD)	78	59	75.6	30	17	12
	Without heart disease (PRHD)	13	6	46.2	2	3	1
All patients with + or ++ activity	With heart disease (RHD)	180	113	62.8	68	26	19
	Without heart disease (PRHD)	50	18	36.0	13	3	2

* None of the patients with severe (+++) rheumatic fever activity escaped without valvular involvement and therefore this group has not been included in this analysis

structure which could be readily moved under the skin over the olecranon process It had all the clinical characteristics of a rheumatic nodule Unfortunately, permission for its biopsy was not obtained At the time the tests were performed and interpreted in the group of feebleminded children, the cardiac status and the medical histories of the patients were not known to us Later, when the histories and physical findings were reviewed it was found that only one of the children had been known to have had rheumatic fever and this one was the patient who had developed the typical subcutaneous nodule He had had rheumatic fever six months previously, and on examination he was found to have the signs of rheumatic heart disease with aortic regurgitation and mitral valve involvement

If, as seems justifiable, the two patients with disseminated lupus erythematosus and the rheumatic fever patient from the feebleminded group are eliminated from the controls, it is evident that tests in 185 individuals

with conditions unrelated to rheumatic fever resulted in nodules in five instances, an incidence of only 2 7 per cent. Furthermore, of the three induced nodules which were examined microscopically only one (from a patient with scarlet fever) was considered to be consistent with a rheumatic nodule.

Relation of the Cardiac Status to Induced Nodule Susceptibility. The relation of the presence and absence of valvular damage to the ease with which nodules could be induced and to the size of the induced nodules is of some interest and is indicated in Table 7. All of the patients with severe (+++) rheumatic fever had evidence of valvular involvement, and therefore this analysis is restricted to those in the quiescent (O) stage and those with mild (+) and moderate (++) rheumatic activity.

In patients in whom the rheumatic process was quiescent, whether or not there was detectable valvular disease, the incidence of induced nodules was low and those nodules which could be induced were small However, in patients with active rheumatic fever, those who had valvular damage (RHD) seemed to develop nodules more readily than did those without detectable cardiac involvement (PRHD) Thus, from the combined data of those with mild (+) and moderate (++) rheumatic activity, it is evident that nodules were successfully induced in 62 8 per cent of those with rheumatic heart disease in contrast to 36.0 per cent of those without cardiac involvement. On the average the induced nodules in the rheumatic heart groups were also slightly larger than those in the group without heart disease

Significance of Chorea in Relation to Induced Nodule Reaction Chorea of varying degree was present at the time of the standard olecranon test in forty-eight patients. The significance of chorea in relation to induced nodule susceptibility is of interest but is difficult to determine in this group because of the many other variables which also might have played a role in regard to the results of the tests. Among these variables are the presence or absence of other rheumatic fever manifestations besides chorea, the presence or absence of valvular involvement, and the severity of the chorea

Thus, an analysis made in relation to cardiac status alone reveals the incidence of induced nodules to be eleven out of nineteen tests (58 per cent) in the patients with rheumatic heart disease in contrast to twelve out of twenty-nine tests (41 per cent) in those without heart involvement In patients with other rheumatic fever manifestations as well as chorea at the time of the test, nodules were successfully induced in twelve out of eighteen (67 per cent) in contrast to an incidence of eleven out of thirty (37 per cent) in those who had chorea without an elevated sedimentation rate or other rheumatic manifestations.

In spite of possible statistical inaccuracy incurred by the small numbers involved, it is of interest to analyze the role of chorea, per se, by dividing the thirty patients who showed chorea as their only manifestation into those with mild chorea and those with moderate or severe chorea In seventeen patients with mild chorea, nodules were successfully induced in four (24 per cent), while in thirteen patients with moderate or severe chorea nodules were induced in seven (54 per cent).

Even when the analysis is restricted still further to those patients without valvular involvement and without other rheumatic fever manifestations

(so-called "pure" chorea), it is observed that nodules were induced in four out of twelve patients with mild chorea (an incidence of 33 per cent) and in four out of nine patients with moderate or severe chorea (an incidence of 44 per cent).

In spite of the small numbers involved, it seems evident from the above

matic Fever It is a general impression that spontaneous nodules do not appear during the first few weeks of an initial attack of rheumatic fever but rather that they tend to occur during the subacute and chronic stages of the disease However, in patients developing recrudescences in the course of convalescence from a previous attack of rheumatic fever we have occasionally observed nodules to develop spontaneously fairly early in the flare-up

Table 8 Relation of Nodule Development to Time Elapsed Since Onset of Rheumatic Fever Recrudescences

TIME OF TEST IN RELATION TO ONSET OF A CLINICAL RECRUDESCENCE	TOTAL TESTS*	INDUCED NODULES	
		Number	Per cent
Within the 1st week	10	7	70
2nd to 3rd week	16	11	69
4th to 8th week	7	6	86
9th to 25th week	18	16	89
TOTAL OF ALL CASES	51	40	78

* All patients used for this analysis had rheumatic heart disease and all had clinical rheumatic fever (++ or +++ activity) at the time that the tests were performed

Therefore, it is of interest to review the results of the standard tests which were performed in patients who had experienced recrudescences of rheumatic fever while under observation in the hospital and to relate the results of the tests to the time which had elapsed since the onset of the recrudescence So that reliable comparisons could be made, the analysis has been restricted to patients who had valvular damage and who had clinical rheumatic fever (either ++ or +++ activity) at the time that the tests were performed From these data, which are presented in Table 8 it is evident that elapsed time, per se was a factor of not much importance in relation to the readiness with which nodules could be induced In these patients, all of whom had clinically active rheumatic fever and valvular damage, nodules were induced in a high percentage of instances at all stages of the recrudescences, even within the first week after onset

We have not had the opportunity to test patients in the early stages of initial attacks of rheumatic fever, and obviously that information collected from recrudescences occurring in patients who just prior to the flare-up still had low grade rheumatic fever, or who had only recently recovered is not necessarily applicable to initial attacks of the disease

Effect of Salicylate Therapy on Induction of Nodules Most rheumatic

fever patients who have spontaneous nodules as a manifestation of their disease also develop involvement of the valves of their hearts In fact, only in rare instances do they escape without detectable valvular damage. Because of this interesting relationship, information as to whether salicylate therapy will prevent the induction of nodules might possibly offer some indirect evidence as to whether similar therapy can be expected to prevent valvular damage Although our experiments were not planned with this objective in mind, a review of the data indicated that in forty-two patients with clinical rheumatic fever (++ or +++ activity) at the time that the tests were performed, information is available as to whether

Table 9 Incidence of Induced Nodules over Anterior Aspect of Knee Compared with Expected Number of Induced Nodules Calculated from Olecranon Test Data

RHEUMATIC ACTIVITY AND CARDIAC STATUS OF PATIENTS TESTED IN KNEES	NUMBER OF TESTS DONE	ACTUAL NUMBER OF INDUCED NODULES	EXPECTED NUMBER OF INDUCED NODULES*
RF = 0, RHD and PRHD	32	0	$32 \times \frac{15\ 2}{100} = 4\ 864$
RF = +, RHD	16	2	$16 \times \frac{52\ 9}{100} = 8\ 464$
RF = +, PRHD	5	0	$5 \times \frac{32\ 4}{100} = 1\ 620$
RF = ++, RHD	25	5	$25 \times \frac{75\ 6}{100} = 18\ 900$
RF = ++, PRHD	2	0	$2 \times \frac{46\ 2}{100} = 0\ 924$
RF = +++, RHD	22	11	$22 \times \frac{85\ 7}{100} = 18\ 854$
TOTAL	102	18	53 626

or not salicylate therapy was being administered In fourteen (82 per cent) of seventeen patients not receiving salicylates, nodules were successfully induced, while in twenty-two (88 per cent) of twenty-five patients receiving the drug, nodules were also induced In most instances salicylates were given orally in the form of aspirin, the dosage usually ranging from 1 to 3 gm daily, an amount sufficient for symptomatic relief.

It is evident from these data that salicylates or, at least, acetylsalicylic acid in small or moderate doses does not prevent the induction of subcutaneous nodules We have no observations on the effect of massive salicylate therapy

The Induction of Nodules at Sites other than the Olecranon Process The original attempt to induce nodules[2] was made with tests in the region of the olecranon process of the elbow because this is the most common site of spontaneously occurring rheumatic fever nodules, for the same reason, most subsequent studies have made use of this same region In order to determine whether or not there was anything peculiar to the subcutaneous tissues of the elbows, observations have also been made on the effect of injecting blood subcutaneously over other bony prominences Most of these additional tests have been performed over the anterior aspect of the knee, but a relatively few tests have also been performed in other regions

Data on a total of 102 knee tests are presented in Table 9 Information is given as to the degree of rheumatic fever activity at the time of the tests, the cardiac status of the patients tested, the number of successfully induced nodules, and, by applying the data furnished in Tables 4 and 7, the number of induced nodules which would have been expected if the knee were as susceptible to the development of induced nodules as is the olecranon process It is evident from the totals given at the bottom of the table that the incidence with which the subcutaneous injection of the patient's own blood over the anterior aspect of the knee induced nodules was on the average about one-third of that which was to be expected had the test been performed over the olecranon process

In seventy-two instances tests were actually performed simultaneously in both the knee and the olecranon process Definitely detectable nodules were induced by thirty of the olecranon tests and only by seven of the knee tests

In addition to these observations, tests with blood were also performed over the spine in six instances, over the internal aspect of the ankle in two instances, over the lateral aspect of the elbow in three instances, and over the forearm distal to the olecranon process in four instances As the result of all of these tests nodules appeared only twice and both of these were in the forearm

From these observations it would appear that subcutaneous tissues over other bony prominences, as well as those over the olecranon process, are also susceptible to the induced nodule reaction but not to the same degree as the olecranon tissues

Induced Nodule Tests Using Saline and Blood "Gently" The standard method of injecting blood subcutaneously over the olecranon process involves inserting the needle through the skin and then directing it into various areas, including the deep tissue close to the bone, and forcing varying amounts of blood into these places This procedure results in distention of tissue spaces and traumatization of the tissues in general

In order to determine whether or not the induced nodule was due to traumatizing effect alone or to something in the blood itself, tests were performed in the usual way but with saline instead of blood, while other tests were done by injecting 2 to 3 cc of blood slowly through a fine needle into one area of the subcutaneous tissue, thereby avoiding widespread trauma as far as possible

In 105 instances among patients with varying degrees of rheumatic fever activity (O to + + +) the standard test was used, but the patient's own blood was injected into one elbow and saline was injected with the same

hyaluronidase. Although studies with this substance* are not yet complete, it is appropriate at this time to summarize some of our observations.[6]

One of the procedures used has involved the subcutaneous injection over the olecranon process of 30 turbidity reducing units of hyaluronidase in a volume of 0 5 cc The injections have usually been repeated in the same area daily or every other day for a total of four to five injections within a period of one week In twenty-four such tests nodules have been successfully induced in eleven instances.

COMMENT

In previous communications[2, 3] the development of nodular structures in a high percentage of rheumatic fever subjects following the subcutaneous injection of blood over the olecranon process of the elbow was described and the clinical and histopathologic similarity of these structures to spontaneous nodules was indicated The numerous observations which have been accumulated during the intervening years and which form the basis of the present report confirm our original impressions

The readiness with which nodules can be induced by the blood injection method shows a strong correlation with rheumatic fever activity. The standard technique was followed by the development of a definite subcutaneous nodule over the olecranon process in 15 2 per cent of 165 patients in whom active rheumatic fever had recently subsided, in 47.5 per cent of patients with low grade (usually subclinical) rheumatic fever, in 71 4 per cent of ninety-one patients with moderately active clinical rheumatic fever, and in 85 7 per cent of fifty-six patients with severe rheumatic fever. In striking contrast to these results was the development of small subcutaneous nodular structures in only five (2 7 per cent) of 185 control subjects who were suffering from conditions unrelated to rheumatic fever.

The development of a definite induced nodule in one of seventy-nine feebleminded children and the subsequent discovery that this boy had had rheumatic fever six months previously which left him with rheumatic heart disease was especially impressive

In a ten-year-old girl, one of two patients suffering from disseminated *lupus erythematosus*, a subcutaneous nodule of moderate size and indistinguishable from rheumatic fever nodules followed a test performed during an acute exacerbation of her illness In view of the fact that this condition as well as rheumatic fever and rheumatoid arthritis belongs to the group of "collagen" diseases and since spontaneous nodules have occasionally been described in disseminated lupus erythematosus, the artificial induction of a nodule in this child is not surprising nor out of line with the hypothesis that subcutaneous nodules are a specific manifestation

In addition to frequency, the size and duration of induced nodules also showed a close correlation with degree and duration of rheumatic activity Thus, in those patients in whom the rheumatic process had seemed to have subsided at the time that the tests were performed, those relatively few nodules which did develop were small and as a rule lasted only one or two weeks On the other hand, in patients with severe and chronic rheumatic fever the induced nodules were on the average much larger, and they often

* Hyaluronidase was supplied through the courtesy of Dr W. Alan Wright of the Schering Corporation

persisted for several months. In fact, in this last group of patients, nodules remaining palpable for six months or more were not uncommon

Among those patients with active rheumatic fever the higher incidence of induced nodules in those with clinically evident valvular damage than in those without apparent cardiac involvement is of interest and, perhaps, is consistent with the hypothesis that the mechanisms involved in the production of subcutaneous nodules and valvular damage are similar.

The successful induction of nodules over the anterior aspect of the knee, although not occurring with as high frequency as in the region of the elbow, indicates that there is nothing peculiar to the subcutaneous tissues overlying the olecranon process. In this connection, it is of interest that spontaneous nodules occur much more commonly over the olecranon process than at other sites

Two sets of observations, although not necessarily relevant to the general purpose of this study, are of interest and worthy of brief comment They are concerned with the induction of nodules in patients with chorea and in patients receiving salicylate therapy In regard to chorea, our limited studies suggest that this condition acts much like any other clinical rheumatic manifestation in so far as it influences susceptibility to induced nodules. If these observations could be extended, they might shed some light on the problem of whether or not chorea is always of rheumatic origin

In regard to salicylates, it appears that these drugs or, at least, acetylsalicylic acid in small to moderate dosage did not interfere with the successful induction of nodules These findings, which are consistent with the observations that spontaneous nodules may also develop in patients receiving salicylates, may have some bearing on the question of the value of salicylate therapy for rheumatic fever

The mechanism by which the subcutaneous injection of blood produces nodules in rheumatic fever patients is of especial interest. Although the studies reported in this communication do not unravel the problem, they perhaps take us a step closer to the solution

The demonstration that the readiness with which nodules can be induced correlates closely with the degree of activity of the rheumatic process suggests as one possibility that an unidentified nodule-stimulating substance is present in the blood of patients with active rheumatic fever and is either absent from the blood of individuals who have recently recovered, or is inhibited by a corresponding antibody or neutralizing substance present in the blood at this stage of the disease Another possible mechanism suggested by these observations is that nodule formation is a reaction to injury and that the reaction of the tissues is conditioned by the rheumatic state of the individual

The higher incidence of induced nodules in quiescent rheumatic fever subjects when fresh citrated blood from highly active rheumatic fever patients was used for the tests than when their own blood was used for the tests at first seemed to confirm the theory that active rheumatic fever blood contains a nodule-stimulating substance However, the subsequent demonstration that citrated blood from healthy young adults was at least as effective as active rheumatic fever blood in stimulating the production of nodules makes this hypothesis less tenable. Furthermore, the failure of convalescent serum to prevent the development of nodules, even when

injected daily into the site of the test, is strong evidence against the existence of antibodies or neutralizing substances for this hypothetical nodule-stimulating substance.

In fact, these various observations are more consistent with the second hypothesis, namely that nodule development is a reaction to trauma and is dependent upon an alteration in tissue reactivity which, in turn, is brought about in some still unexplained way by the rheumatic state. The higher incidence of induced nodules when blood was injected with the standard traumatizing technique than when it was injected slowly through a fine needle, and the development of nodules following even the injection of saline in such a way as to distend and disrupt the subcutaneous tissues, would seem to be consistent with the theory that rheumatic fever produces an alteration in the reactivity of the fibrous tissue In connection with the interpretation of the saline tests, the possibility of nodules developing as a result of some substance in the patient's own blood can not be entirely ruled out since the traumatizing technique which was used also caused some bleeding into the subcutaneous tissues.

That enzymes may play a role in the histopathologic processes of rheumatic fever is suggested by the observations of Mirsky[7] that subcutaneous nodules could be induced in rheumatic fever subjects by the subcutaneous injection of trypsin, and by our own more recent studies in which the subcutaneous injection of hyaluronidase also induced nodules in certain patients. However, it is also possible that trypsin and hyaluronidase act in a nonspecific way and that they merely cause tissue injury which, in turn, in the presence of active rheumatic fever, sets off the nodule reaction

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ABSTRACTS

INDUCTION OF CARDIAC LESIONS, RESEMBLING THOSE OF RHEUMATIC FEVER, IN RABBITS SICKENING AFTER REPEATED SKIN INFECTIONS WITH GROUP A STREPTOCOCCUS

GEORGE E. MURPHY AND HOMER F. SWIFT

those sacrificed while sick, there were found focal collagenous connective tissue alterations in vascular adventitia, valves, mural endocardium, epicardium and in myocardial interstitium unrelated to arteries or veins. Interspersed in fields of fibrinoid collagen were nodular collections of large, irregularly shaped cells, often with abundant, finely granular, basophilic, indistinctly outlined cytoplasm. The variously shaped vesicular nuclei, single or multiple, had sharply defined mem-

sulcus and valvular endocardial and subendocardial cells formed palisades containing numerous multinucleated giant cells. A variety of coronary arterial lesions were found, but panarteritis of the periarteritis nodosa type was not present. Neither bacteria nor inclusion bodies were seen. The lesions were found in only a small portion of rabbits sickening after multiple, successive, cutaneous infection with several types of group A streptococci. They were not found in rabbits sacrificed or suc-

travenous inoculation with one of several types of group A streptococci.

PUBLIC HEALTH ASPECTS OF RHEUMATIC FEVER

DAVID D. RUTSTEIN

Rheumatic fever and rheumatic heart disease are public health problems because attacks of rheumatic fever are often precipitated by an infectious microorganism, the beta hemolytic streptococcus, and because this disease complex is a chronic one, occurring primarily in lower income groups and necessitating utilization of many community facilities.

The prevention of beta hemolytic streptococcal infection in rheumatic patients

can be accomplished by protection of patients in hospitals against exposure to this microorganism, avoidance of contact with others known to be infected with the beta hemolytic streptococcus, prevention of airborne infection and prophylaxis with sulfonamide drugs or penicillin

The chronic nature of rheumatic disease and its predilection for younger age groups necessitates cooperative efforts on the part of many community agencies, such as has been effectively demonstrated in tuberculosis programs It is possible to set up public health programs which will coordinate efficiently the activities of these various agencies for the benefit of the patient and his family and for the conservation of community resources The mechanism for such coordination is the registry

[illegible]

may safely be used for prophylaxis against recurrent attacks of acute rheumatic fever, that cases of subacute bacterial endocarditis will be prevented by assuring the use of sulfonamide drugs or penicillin prior to tooth extraction or operation on the upper respiratory tract, and that young patients suffering from rheumatic heart disease may receive vocational training so that they may become useful citizens instead of public charges.

DISCUSSION*

There is much we can do, through the application of public health methods, to lower the incidence of recurrent attacks of rheumatic fever. We can lessen disability, prevent untimely death, provide many years of happy living, and keep economically independent an important number of those who are victims of the disease

Only a short while ago one would not have had the temerity to think of rheu- [illegible]

quences and its mortality with a stoic fatalism The medical profession itself could hardly see a strategy inclusive of more than increased attention to research and the application of current knowledge through the individual physician-patient relationship

Stimulated, however, by the enormity of the problem and the meager resources available for solving it, a number of leaders in the field resolved to remedy the situation There is no necessity to review for this audience the pioneer work done [illegible] Academy of Pedia- [illegible]

additional weapon for the improvement of our attack on rheumatic fever.

It is highly important in this undertaking to proceed only after a careful consid-

* By John W Ferree.

eration of what should be the philosophy underlying our efforts I feel, and I believe Doctor Rutstein shares this feeling, that we must accept and then act on certain basic premises if we are to be successful I should like to discuss two that ap-

only quote the proposed objectives of this Commission to indicate clearly how compatible they are with what we concerned with rheumatic fever will probably con-

socially useful and economically productive place in the community.

"B To define the problems arising from chronic illness among all age groups, with full realization of its social as well as its medical aspects.

"C To coordinate separate programs for specific diseases with a general program designed to meet more effectively the needs which are common to all the chronically ill

"D To clarify the interrelationship of professional groups and agencies now working in the field

"E To stimulate in every state and locality a well-rounded plan for the prevention and control of chronic disease and for the care and rehabilitation of the chronically ill"

I stress the necessity for conceiving of rheumatic fever as a chronic disease because a successful public health attack on it will require us to provide many of the services and facilities

we were to attempt a public health attack on rheumatic fever set apart from the

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to contribute to the welfare of the rheumatic fever patient.

The physician has an obligation to learn better and to practice the art of counselling with his patients and their parents to the end that they may know how to protect themselves from unnecessary complications, live willingly up to but not

beyond their capacities and know how to make the best possible use of available facilities and services There is a further job to do and that is to see to it that people in general know enough about rheumatic fever to visit the physician early

done improperly or not done than to condemn the principle of education

I believe that as we enlarge our understanding and application of public health methods in the control of rheumatic fever, we will gain an increasing confidence in their usefulness and a genuine satisfaction in the results.

RHEUMATOID ARTHRITIS

FACTORS ASSOCIATED WITH THE ONSET OF RHEUMATOID ARTHRITIS

A Statistical Study of 293 Patients and Controls

CHARLES L. SHORT, NATHAN R. ABRAMS AND PHILIP E. SARTWELL

CLINICAL MATERIAL

The data presented are derived from a series of 293 patients with rheumatoid arthritis who represent consecutive admissions to the medical wards of the Massachusetts General Hospital from 1930 to 1936. These patients may be considered essentially unselected except that their disease was severe enough to warrant hospital admission and that children under twelve, who were cared for on a separate pediatric service, are not included. In each instance the diagnosis of rheumatoid arthritis was evident from the usual clinical and laboratory criteria, and other joint conditions were carefully excluded. Patients with rheumatoid spondylitis were included in the series whether or not peripheral arthritis was also present. We plan to pursue the study as far as possible through the life of each patient. Preliminary results in this follow-up study have already been reported.[1]

Comparisons have been made with a control group of 293 persons without joint disease, in order to determine the significance of possible etiologic factors in the family and past histories and of the incidence of certain constitutional symptoms and signs. This group was selected to correspond with the arthritic patients in sex distribution, age grouping, economic status and geographic location.

SEX INCIDENCE

Females outnumbered males in our series by nearly two to one. The underlying cause or causes of this generally accepted finding are as yet unknown. That the disease attacks females at a much earlier age than males has not been demonstrated, and that females inherit a susceptibility to the disease has yet to be proven by genetic studies. The sex distribution in many other diseases is equally striking and incapable of explanation. I may mention merely the predisposition of males to gout and hemochromatosis and of females to gallbladder and thyroid disease. When rheumatoid

tion of the disease as a whole. On the other hand, chorea and mitral stenosis occur much more frequently in females, although the incidence of all manifestations of rheumatic fever does not favor either sex.

AGE AT ONSET

Opinions and figures vary widely in regard to the distribution of the age at onset in rheumatoid arthritis. Little significance can be attached to such

data without taking into consideration the age distribution of the population at risk In Table 11, the males are divided into five-year groups according to the age at which definite joint involvement appeared Actual frequencies are compared with expected frequencies based on the census figures for the distribution of the population in Massachusetts in 1930 The onset was

Table 11 Age at Onset—Males

AGE	CENSUS POPULATION IN THOUSANDS	CASES OBSERVED	CASES EXPECTED
15–19	181 0	11	12 2
20–24	163 1	14	11 0
25–29	153 3	16	10.3
30–34	154 0	15	10 4
35–39	163 5	10	11 0
40–44	147 5	8	10 0
45–49	130 7	11	8 8
50–59	209 7	6	14 1
60–74	166 1	8	11 2
TOTALS	1468 9	99	99

most common at the ages of 25–29. The chi-square test indicates no significant departure from the Massachusetts population In females (Table 12), the marked increase in the age group fifty to fifty-four and the decrease over the age of sixty caused a difference which can hardly be accounted for by chance These results are in general agreement with those of Sclater,[2]

Table 12 Age at Onset—Females

AGE	CENSUS POPULATION IN THOUSANDS	CASES OBSERVED	CASES EXPECTED
15–19	185 2	16	20 8
20–24	182 5	22	20 4
25–29	170 8	19	19 1
30–34	167 5	18	18 7
35–39	172 0	19	19 2
40–44	148 5	15	16 6
45–49	134 8	16	15 1
50–54	120 3	28	13 5
55–59	101 6	15	11.4
60–74	189 7	8	21.2
TOTALS	1572.9	176	176

who has made a similar study in respect to the population of Scotland, if allowance is made for the exclusion of patients with spondylitis from his series. The traditional view that rheumatoid arthritis is mainly a disease of young women is not supported in either study. The falling off in the older age groups, however, a tendency toward which is also seen in males, may be only apparent, since joint disease in older persons seems more likely to

be accepted as one of the inevitable features of senility and not to demand hospital admission

RELATION OF ONSET TO MENOPAUSE

The increased incidence of the onset of rheumatoid arthritis in females between the ages of fifty and fifty-four immediately suggests an influence of the menopause. In our study, however, there is little difference between patients and controls in respect to the age of menopause. As an additional check, a comparison has also been made with a representative series of American women [3] Thus, while Olch[4] has shown that the menopause occurs later than normally in women with breast cancer, such is not the case in rheumatoid arthritis, nor is an early menopause associated as stated by Fox.[5] While there is no correlation in our series between the age at onset of the arthritis and the age of natural menopause, an apparent relationship exists between the age at onset and age of artificial menopause in fifteen patients,

Table 13 Relationship of Onset of Arthritis to Menopause

GROUP	NUMBER IN GROUP	MEAN INTERVAL BETWEEN ONSET AND MENOPAUSE	ONSET WITHIN TWO YEARS BEFORE OR AFTER MENOPAUSE	ONSET IN SAME YEAR AS MENOPAUSE
		Years	Per cent	Per cent
Whole group	95	7 5	32 7	10 5
Natural menopause	80	8 0	28 7	10 0
Artificial menopause	15	5 0	53 3 (20 0 after)	13 3
Group with onset of arthritis from ages 50 to 54	28	3 7	39 4	10 7

the coefficient of correlation is + 72 ± 14 In two patients the arthritis began within six months of the sterilizing operation. The relationship seems less close, however, when we note that in five patients, the arthritis preceded the menopause and in another five patients from eight to sixteen years elapsed between menopause and onset of arthritis Table 13 demonstrates no close relationship between the start of the arthritis and the last menstrual period in those women with a natural or artificial menopause, nor in the relatively large group with onset from ages fifty to fifty-four We may conclude, then, that the high incidence of rheumatoid arthritis in women in the fifth and sixth decades, if on an endocrinologic basis, must be accounted for by other factors than the actual cessation of menstruation

FAMILIAL INCIDENCE

The data pertaining to family history in rheumatoid arthritis were obtained by questioning both patients and controls. One objection to the acceptance of significant differences obtained in this manner is the likelihood that an arthritic patient may be more aware of articular disease in his family than a control In this study we were interested in constitutional as well as joint disease in an attempt to determine whether or not the rheu-

matoid stock was generally vulnerable. No significant difference was observed in frequency of diseases of the heart, blood vessels and kidney, cancer, diabetes mellitus, allergic diseases and migraine Table 14 shows that rheumatoid arthritis occurred more often in the families of arthritic patients than in the families of controls In four of the thirty-five families, two additional cases were reported, and in five families, three–figures higher than would be expected on the basis of probability. Even more striking instances of a large number of cases in a single family are known to occur. An interesting finding, in view of the relationship often postulated between rheumatoid arthritis and rheumatic fever, is the significantly higher incidence of rheumatic fever in the families of patients compared to controls The two diseases occurred together in the same family (in addition to the patient) in only five instances, hardly more than would be expected by chance. It would seem reasonable from the data presented to assume that a familial tendency exists in rheumatoid arthritis, but no conclusions can be drawn as to the relative influence of environment, contagion or

Table 14 Incidence of Rheumatoid Arthritis and Rheumatic Fever in Families of Arthritics and Controls

	NUMBER OF FAMILIES WITH ONE OR MORE CASES (EXCLUSIVE OF PATIENT)		PERCENTAGE INCIDENCE		DIFFERENCE IN INCIDENCE
	Patients	Controls	Patients	Controls	
Rheumatoid arthritis	35	15	11 9	5 1	6 8±2 3
Rheumatic fever	34	9	11 6	3 1	8.5±2 1

heredity until carefully controlled genetic studies can be performed, including questioning and examination of all available members of the patients' families

INCIDENCE OF ALLERGIC MANIFESTATIONS

If rheumatoid arthritis is of allergic origin, we should expect, by analogy with known allergic disease, an increased familial incidence of asthma, hay fever or urticaria and the coexistence of these same manifestations in a significant number of the patients themselves Fifty-four of the patients (18 5 per cent) gave family histories which showed asthma, hay fever or urticaria, and forty-six patients (15 9 per cent) reported these diseases in their personal histories Fifty-five of the controls (18.7 per cent) reported these diseases in their family histories and forty of the controls (13 6 per cent) reported the diseases in their personal histories. Thus, in our series no essential difference was found between patients and controls in these two respects.

LOCATION OF INITIAL JOINT INVOLVEMENT

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metry was apparent from the beginning in 70 per cent of 262 patients with onset in peripheral joints, while the spine was primarily affected in the remaining thirty-one. Large and small joints (which included the hands, *feet and wrists) were first affected with about equal frequency* (Table 15). That rheumatoid arthritis should not be considered a form of joint disease which initially attacks the small articulations of the hands and feet is also shown, since such an onset was present in less than a third of the patients

Table 15 Incidence of Initial Involvement of Groups of Joints

GROUPS OF JOINTS	NUMBER OF PATIENTS	PER CENT
Small (hands, feet, wrists)	115	39 3
Large	124	42 3
Spine	31	10 6
Large and small	23	7 8
TOTAL	293	100 0
Hands and/or feet	89	30 4

Contrary to opinion expressed in the literature, joints of the legs were more frequently affected in the beginning than those of the upper extremities, with this difference more marked in males In about one-sixth of the present series, the disease first appeared in a single joint, most often the knee As noted by others, this monarticular stage might persist and occasion difficulty in formulating the final diagnosis In only three patients, however, was the process monarticular on admission to the hospital Table 16 demonstrates

Table 16 Joints First Involved in Patients Classified in Spondylitis Group on Admission

JOINTS	NUMBER OF PATIENTS	PER CENT
Spine	21	53 8
Feet	5	12 6
Hips	4	10 3
Knees	4	10 3
Hips and knees	2	5 2
Ankles hips and knees	1	2 6
Temporomandibular	1	2 6
Shoulders	1	2 6
TOTAL	39	100 0

that in about one-half of the group with spondylitis on admission, the process began in one or more peripheral joints, almost invariably of the lower extremities

PRODROMATA AND PRECIPITATING FACTORS

In the literature on rheumatoid arthritis, allusion has frequently been made to a prodromal period preceding the onset of arthritis[6 7 8] Of six prodromal symptoms studied in our patients, fatigue and appetite loss occurred with significantly greater frequency in patients than controls

Skeletal pain, sensory disturbance and crepitus were elicited from an equal number of controls, as was accentuation of any of these symptoms by changes in weather. Fatigue and appetite loss were less common as prodromal symptoms in males than in females and in patients with spinal involvement

As shown in Table 17, about one-half of the patients gave a history of one or more precipitating factors preceding the onset of a persistent arthritis

Table 17 Incidence of Precipitating Factors Preceding Onset of the Arthritis

PRECIPITATING FACTOR	NUMBER OF PATIENTS	PER CENT
Strain, mental, physical or both	81	27 6
Infection	49	16 7
Exposure to cold or dampness	31	10 6
Surgical operation	16	5 5
Trauma	15	5 1
TOTALS	192	65.5
Patients with one or more precipitating factors	144	49 3
Patients without precipitating factors	149	50 7
TOTALS	293	100 0

A number gave a history of two or more, so that a total of 192 factors was elicited from 144 patients The most common combination was strain of long duration, with the onset immediately preceded by an infection, operation

Table 18. Incidence of Prodromal Symptoms and Precipitating Factors in 85 Patients with Onset Dating Back a Year or Less

GROUP	NUMBER OF PATIENTS	PER CENT
Neither prodromata nor precipitants	14	16 5
Prodromata alone	21	24 8
Precipitants alone	17	20 0
Both prodromata and precipitants	33*	38 7
TOTALS	85	100 0

* Prodromata first in 80%

or injury. Under strain, both mental and physical types are included. The experience of ourselves and others since these patients were questioned would indicate that a much higher incidence of mental strain would have been obtained had a special search been made for precipitating emotional and environmental factors Infection, nearly always of the upper respiratory tract, preceded an onset which was often acute in about one-sixth of the cases Trauma was rarely a factor, but our data show that it may have

been operative in determining the initial localization of the arthritis While the disease began in five females within one month of delivery, it started during pregnancy in only one patient.

The onset dated back a year or less in eighty-five of our patients, a group chosen as most likely to reveal accurate information of the events preceding the onset of the arthritis As shown in Table 18, the onset in only fourteen cases appeared out of an entirely clear sky with neither prodromata nor precipitating factors. In twenty-one, prodromal symptoms alone preceded, while in seventeen the arthritis followed one or more of the precipitating factors listed above, without a definite prodromal period. Of the remaining thirty-three patients whose history contained both precipitants and prodomata, in twenty-one the sequence of events leading up to the onset could be reasonably well outlined In the majority of instances, what may be regarded as constitutional features of the disease were already present when the acute infection or other disturbance apparently initiated the stage of actual arthritis. These data suggest that prodromal symptoms may mark the real onset and that so-called precipitating factors merely determine a more easily recognizable phase, with articular localization of the morbid process

COMMENT

There are no formal conclusions to be derived from these fragments of a numerical approach to the study of a chronic disease of unknown etiology The analysis is still in progress and as many as possible of the patients are being followed At a later date, it is hoped to present the material as a whole as a contribution to the clinical description of rheumatoid arthritis

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A STATISTICAL ANALYSIS OF 1000 CASES OF RHEUMA TOID ARTHRITIS IN RELATION TO INSIDIOUS AN ACUTE ONSET, MENOPAUSE, PREGNANCY, PSORIASIS ANKYLOSING SPONDYLITIS AND STILL'S DISEASE*

SVEND CLEMMESEN AND ELSE ARNSØ

The average age at onset of rheumatoid arthritis still presents certain statistical problems, and the following questions arise:

1. Is there any difference in age of onset between rheumatoid arthritis of insidious onset and rheumatoid arthritis developed after a condition simulating rheumatic fever (each sex evaluated separately)?

2. Are women at the average menopause age more exposed to rheumatoid arthritis than women at other ages and, if so, does this hold good for both types of rheumatoid arthritis?

3 Is rheumatoid arthritis more or less common in the younger than in the advanced age groups, when a comparison is made with the age distribution of the population?

4. Is it possible through clinical statements to characterize special differing types of rheumatoid arthritis combined with psoriasis, ankylosing spondylitis and Still's disease?

5 Can anything be said concerning the influence of pregnancy on rheumatoid arthritis?

Most of the statistics up to date divide the materials only into ten-year periods, and very often men and women are counted together in one group in order to make the material large enough Most materials mix rheumatoid arthritis of insidious onset with rheumatoid arthritis after so-called rheumatic fever and in addition do not exclude more special types such as Reiter's disease, ankylosing spondylitis, or rheumatoid arthritis combined with psoriasis, syphilis, etc Materials comprising insured persons do not as a rule include rheumatoid arthritis of old age. Thus, few of these prior studies can contribute directly to a final answer to the questions cited

CLINICAL MATERIAL

The following analysis comprises all cases of chronic polyarthritis, registered in the Department of Physical Medicine of the Municipal Hospital of Copenhagen during the years 1938 to 1947. In 1938 Dr. Clemmesen planned a punch-card registration of all polyarthritis patients in the Department of Physical Medicine. Since then 1190 polyarthritis patients have been entered in a central card index and numbered consecutively.

In recording the cases particular care has been taken to get the most precise details for the various headings. Where this has not been possible, and in cases where an intercurrent disease has complicated the pathologic picture, the card has been punched for special complications.

In this way it will be possible, when preparing the material, to pick out

* From the Department of Physical Medicine of the Municipal Hospital, Copenhagen
his study was aided by a grant to Dr. Clemmesen from the *Medicinalfabriken Ferrosan* nd by a grant to Dr Arnsø from the *Rigsforeningen til Bekæmpelse af de rheumatiske gdomme*

such cards in order to determine whether they should be included in the examination in question

The records were obtained from the following sources in-patients in the Department of Physical Medicine, patients in other departments of the Municipal Hospital, when specialists from the Department of Physical Medicine have been called in, out-patients from the clinic of the Department of Physical Medicine, and some private patients of Dr. Clemmesen's.

As the Municipal Hospital is a regional hospital for the City of Copenhagen and the Department of Physical Medicine commands an equal number of beds for men and women as well as a large out-patient clinic, we have a fairly representative cross-section of arthritis patients in Copen-

Table 19 Classifications and Sex Incidence of Forms of Polyarthritis among 1190 Patients in Copenhagen

DIAGNOSIS	NUMBER OF CASES IN EACH GROUP		TOTAL	PERCENTAGE SEX INCIDENCE	
	Women	Men		Women	Men
Rheumatoid arthritis of insidious onset	521	187	708	73 6	26 4
Rheumatoid arthritis developed after rheumatic fever	110	31	141	78 1	21 9
Rheumatoid arthritis developed after vaccination, hepatitis, enteritis, etc	13	11	24	54 1	45 9
Rheumatoid arthritis combined with positive Wassermann test	27	21	48	56 3	43 7
[illegible]	23	8	31	74 2	25 8
[illegible]	10	3	13	76 7	23 3
[illegible]	12	18	60	20	80
[illegible]	35	15	50	70	30
[illegible]	2	48	50	4	96
Still's disease	15	4	19	78 9	21 1
Poncet's disease	3	4	7	42 9	57 1
Ankylosing spondylitis combined with rheumatoid arthritis	0	18	18	0	100 0
Ankylosing spondylitis	6	15	21	28 6	71 4
TOTAL	777	413	1190	65 3	34 7

hagen—with some reservation, however, in the case of children, who are usually sent to municipal children's hospitals Consequently we should be able, at least concerning the cases developed after the age of fifteen, to undertake a direct comparison between the age at onset in our patients and the age distribution of the population of Copenhagen Practically all cases of our material developed during the years 1930 to 1947. By comparing the age at onset with the age distribution of the population of any given year from 1930 to 1947 we could not escape a fundamental error By an examination of the various age distributions of the population, it has been found that the age distribution of 1945, when compared with the age at onset, will more than that of any other year tend to diminish the peaks found in the curves of "age at onset" and thus minimize this experimental error

Table 19 indicates the classification used, the number of cases and the sex incidence of the different groups All the diagnoses have been made by the authors personally on the criteria generally used

A STATISTICAL ANALYSIS OF 1000 CASES OF RHEUMATOID ARTHRITIS IN RELATION TO INSIDIOUS AND ACUTE ONSET, MENOPAUSE, PREGNANCY, PSORIASIS, ANKYLOSING SPONDYLITIS AND STILL'S DISEASE*

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Rheumatoid arthritis combined with positive Wassermann test	27	21	48	56 3	43 7
Unclassifiable polyarthritis	23	8	31	74 2	25 8
Syphilitic polyarthritis	10	3	13	76 7	23 3
Chronic gonorrheal polyarthritis	12	48	60	20	80
Rheumatoid arthritis combined with psoriasis	35	15	50	70	30
Reiter's disease	2	18	50	4	96
Still s disease	15	4	19	78 9	21 1
Poncet's disease	3	4	7	42 9	57 1
Ankylosing spondylitis combined with rheumatoid arthritis	0	18	18	0	100 0
Ankylosing spondylitis	6	15	21	28 6	71 4
TOTAL	777	413	1190	65 3	34 7

hagen—with some reservation, however, in the case of children, who are usually sent to municipal children's hospitals Consequently we should be able, at least concerning the cases developed after the age of fifteen, to undertake a direct comparison between the age at onset in our patients and the age distribution of the population of Copenhagen Practically all cases of our material developed during the years 1930 to 1947 By comparing the age at onset with the age distribution of the population of any given year from 1930 to 1947 we could not escape a fundamental error By an examination of the various age distributions of the population, it has been found that the age distribution of 1945, when compared with the age at onset, will more than that of any other year tend to diminish the peaks found in the curves of "age at onset" and thus minimize this experimental error

Table 19 indicates the classification used, the number of cases and the sex incidence of the different groups All the diagnoses have been made by the authors personally on the criteria generally used.

The terms "rheumatoid arthritis of insidious onset" and "rheumatoid arthritis developed after rheumatic fever" need some further explanation. The question whether rheumatic fever can develop into rheumatoid arthritis is still open. As early as 1676 Sydenham[1] noted that rheumatic fever might result in chronic polyarthritis and thus cripple a patient for life Later investigators[2–6] have taken the view that rheumatic fever might develop into rheumatoid arthritis. Others, in particular American and English authors,[7–9] would not support this suggestion In the present statistical approach we have assumed that rheumatic fever might precipitate or result in rheumatoid arthritis, and consequently a distinction has been made between two types of rheumatoid arthritis. The one is the type most often met, with insidious onset and often with a symmetric affection of fingerjoints, the other, called "rheumatoid arthritis of acute onset," is the one developed after a condition simulating (if not identical with) rheumatic fever This group includes all cases of rheumatoid arthritis arising acutely with a high fever in connection with some infection of the upper respiratory tract and continuing for more than three months As shown in *Table 19, the sex distribution of the two types is nearly the same, i e*, nearly 75 per cent women to 25 per cent men

AGE AT ONSET

Figure 3 shows the age distribution of the population of Copenhagen compared with the age distribution of [illegible] patients with rheumatoid arthritis. Of [illegible] (73 per cent women) were of insidiou[illegible] women) developed after so-called rheumatic fever.

This figure shows how the method of counting men and women together in ten-year groups blurs all the details, especially the influence of the menopause It will be observed that there are more cases in the older age groups than should be expected if the distribution had been equal in all age groups of the general population.

Figure 4 comprises the same material divided into five-year groups, men and women being included in one group The figure reveals a twin peak, which is an unusual statistical phenomenon

Figure 5 shows the same material again in five-year groups, in which, however, men and women are separated and compared The twin peak is found again in the female group, and in the male group an extraordinary new peak is found after age sixty

Figure 6 shows the age distribution of female patients with insidious rheumatoid arthritis The double peak is found again One peak occurs between ages thirty and forty and another and greater one between ages forty-five and fifty-five As a whole, fewer cases of rheumatoid arthritis are found before age thirty, and more in the older age groups, than would be expected from a study of age groups in the general population.

Figure 7 shows the age distribution of women with rheumatoid arthritis which developed after so-called rheumatic fever, with a significant peak between ages thirty-five and forty and a smaller one between ages fifty and sixty. The significance of the smaller peak, however, may be doubted

[illegible] arthritis of

characteristic feature is the accumulation of cases between ages s[…] seventy-five, i e, an old-age rheumatoid arthritis in men[10-13] […] evaluation of this group by Porsman* seems to indicate a particular […] prognosis and somewhat subacute start, with joint affection of the […]ders.

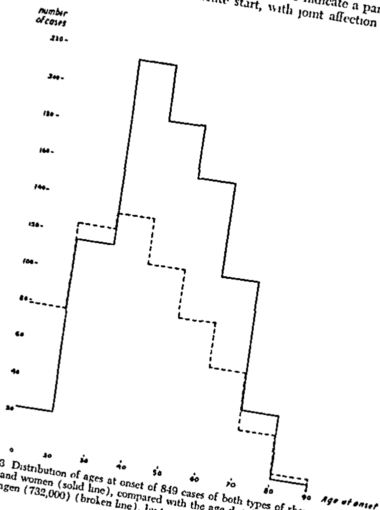


Fig 3 Distribution of ages at onset of 849 cases of both types of rheumatoid arthritis in men and women (solid line), compared with the age distribution of the population of Copenhagen (732,000) (broken line), by ten-year periods

The number of men (forty-three cases) in whom rheumatoid arthritis developed after so-called rheumatic fever is too small to be significant

Figure 9 illustrates the most important statistical observation found in the entire material and might indicate the cause of the double peak. All the female patients have been questioned as to the time of onset of their menopause, by which we mean in this paper, the stopping of the menses The curve showing the statistical menopausal distribution suggests that the menopause is an important factor in the onset of rheumatoid arthritis

* Preliminary communication

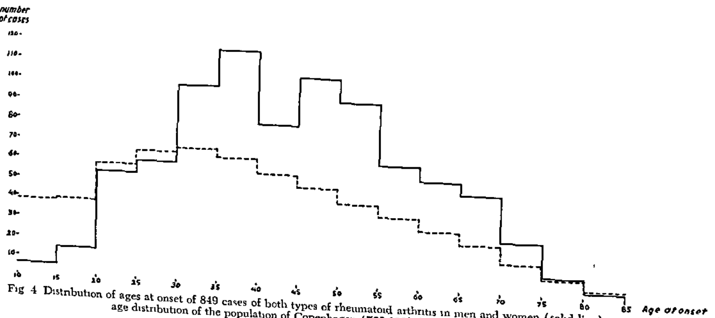


Fig 4 Distribution of ages at onset of 849 cases of both types of rheumatoid arthritis in men and women (solid line), compared with the age distribution of the population of Copenhagen (732,000) (broken line), by five-year periods.

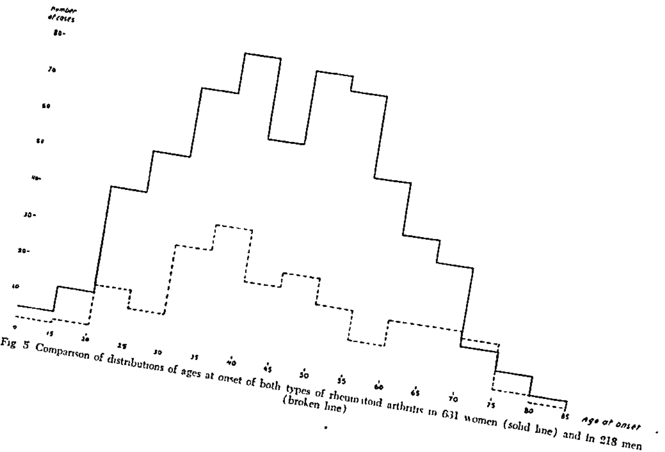


Fig 5 Comparison of distributions of ages at onset of both types of rheumatoid arthritis in 631 women (solid line) and in 218 men (broken line)

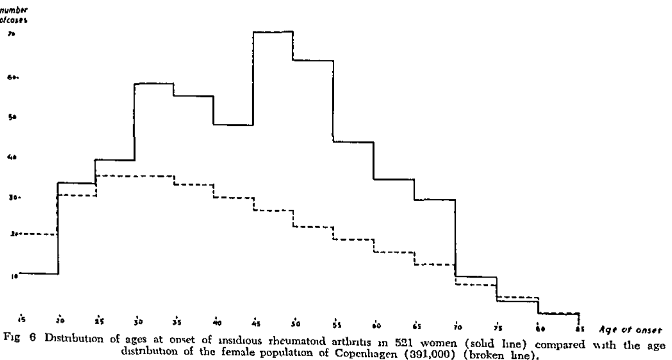


Fig 6 Distribution of ages at onset of insidious rheumatoid arthritis in 521 women (solid line) compared with the age distribution of the female population of Copenhagen (391,000) (broken line).

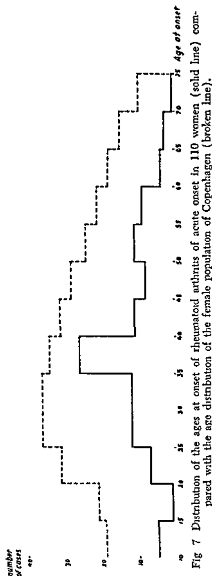


Fig 7 Distribution of the ages at onset of rheumatoid arthritis of acute onset in 110 women (solid line) compared with the age distribution of the female population of Copenhagen (broken line).

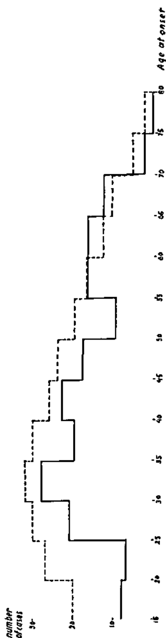


Fig 8. Distribution of ages at onset of insidious rheumatoid arthritis in 187 men (solid line) compared with the age distribution of the male population of Copenhagen (341,000) (broken line).

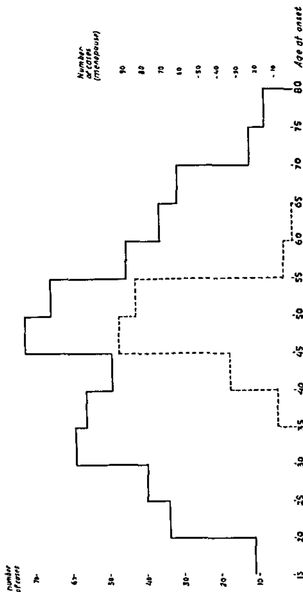


Fig 9 Distribution of ages at onset of insidious rheumatoid arthritis in 521 women (solid line) compared with the distribution of ages at onset of menopause in 231 of the same group (broken line).

of insidious type However, we found that rheumatoid arthritis which developed after rheumatic fever appears to begin more often before the age of forty. As seen from the curves, the age at onset differed markedly in female cases of the two types of rheumatoid arthritis.

Statistical analysis of the results of the antistreptolysin test showed that for rheumatoid arthritis of insidious onset it was positive in only 13 per cent of the cases, while in rheumatoid arthritis developed after so-called rheumatic fever it was positive in 36 per cent of the cases Taking into consideration the fact that the serum was not tested in the acute phase, but most often several years afterwards, these results may indicate that hemolytic streptococci play a certain role by precipitating or complicating this type of rheumatoid arthritis This agrees with the conception, which has grown during our experience, that the factors inducing an aggravation of the insidious type of the disease most often are menopause, lactation, operations and roentgen irradiation on endocrine organs, while in rheumatoid arthritis developed after an acute onset the aggravations most often are observed after tonsillitis, sinusitis, or some other intercurrent infection

Affections of the heart were found (either by roentgenography or electrocardiography) in 5 per cent of insidious rheumatoid arthritis cases and in 7 per cent of cases of rheumatoid arthritis of acute onset. Those figures are not wholly reliable, however, since the heart had not been satisfactorily examined in all the patients.

INFLUENCE OF MENOPAUSE

Garrod,[8] who found the same accumulation of cases of rheumatoid ar-

ages of thirty-five and sixty, sixty of these cases (20 5 per cent) developed within a year before or after their real menopause

COMBINATION OF RHEUMATOID ARTHRITIS WITH PSORIASIS

This combination was found in fifty cases out of 1190 (4 2 per cent). The sex incidence was 70 per cent women to 30 per cent men Wassmann,[11] who studied 10,000 case records from a medical department in Copenhagen—patients suffering from various internal diseases, arthritis not included—found that 0 43 per cent of those patients suffered from psoriasis He believes that this association is significant and not a coincident occurrence of two common diseases

Minute analysis made by Dalkier* showed that, as Hench[15] has emphasized, a tendency exists toward lesions in the terminal and middle joints of the fingers and toes Further, a tendency to marked and rather suddenly destructive joint changes of a whole epiphysis was observed. In some contradiction to this, the roentgenologic changes in many cases were more similar to the picture found in gout and osteoarthritis than to that found in rheumatoid arthritis Osteophytes were more marked and the decalcification not so pronounced as in rheumatoid arthritis

INCIDENCE OF ANKYLOSING SPONDYLITIS

This condition was met with in thirty-nine cases, thirty-three men and six women In the male cases, 38 per cent had developed between the ages

* Preliminary communication

of ten and thirty, 32 per cent between ages thirty and forty, and 30 p cent between ages forty and fifty-five The six female cases developed b tween the ages of nineteen and thirty-five. In eighteen cases the disea was combined with rheumatoid arthritis, and those patients were all me

Until further evidence, these data, as distinct from the female sex facto dominating rheumatoid arthritis, indicate a different pathology in th two diseases Further, the lack of nodules, the lack of benefit from gol therapy and a tendency to ligamentous calcifications (as emphasized by Gibson[16]) supports this view In two cases out of thirty-nine, ankylosing spondylitis was combined with psoriasis, Dawson and Tyson[17] found three cases of typical ankylosing spondylitis combined with psoriasis and Aalvik[18] found this combination in two cases out of a series of twenty

INCIDENCE OF STILL'S DISEASE

Still's disease was met with in nineteen out of 1190 cases of chronic polyarthritis (1 6 per cent) Minute analysis made by Sury* of 150 cases of rheumatoid arthritis developed before the age of twenty (this material comprises patients from all hospitals in Copenhagen during the years 1920 to 1948), indicates that among the prevailing features were tendency to involvement of the greater joints, lack of symmetry, and progression from the central to the peripheral joints Iritis was common. The sex distribution was 58 per cent women and 42 per cent men

INFLUENCE OF PREGNANCY, DELIVERY AND LACTATION

Pregnancy, delivery and lactation have often been suggested as etiologic or precipitating factors in rheumatoid arthritis Charcot[2] emphasized the influence of prolonged lactation Five hundred and twenty-one cases of insidious rheumatoid arthritis have been analyzed with a view to the influence of these factors Thirty-five cases (6 7 per cent) had developed or grown worse after delivery, in sixteen of those cases lactation seemed to be the accelerating factor Seven cases grew worse during pregnancy, but as a rule the symptoms improved only during pregnancy. In a few cases delivery the symptoms were just as bad or worse than before pregnancy and after The numbers reported are too small to draw any significant conclusions

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HEREDITY IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS

ROBERT M STECHER, WALTER M SOLOMON AND RALPH WOLPAW

Although the exact primary cause of rheumatoid arthritis is not known, several contributory or precipitating influences have been recognized. Every experienced rheumatologist will recall instances in which rheumatoid arthritis has been initiated by infection, chilling, severe bodily injury, surgical operation, emotional strain or pregnancy. He will recognize from the study of massed data that susceptibility to the disease is influenced by age, the incidence being highest between ages twenty and forty, and, by sex, the disease being twice as common in women as in men.

Heredity plays an important role in several forms of joint disease. For instance, it is thought that only a small portion of the population can develop gout—that portion who are born with, or develop early, idiopathic hyperuricemia Susceptible individuals can thus be recognized. It is also believed that 30 per cent of all women inherit susceptibility to the development of Heberden's nodes. The age at which they arise depends, in part at least, upon the menopause. Susceptible individuals cannot be recognized until the disease appears Rheumatic fever runs in families but develops only after exposure to streptococci or other bacteria

CLINICAL MATERIAL

Heredity in rheumatoid arthritis and rheumatoid spondylitis was investigated as follows· Family histories regarding rheumatoid arthritis and rheumatoid spondylitis were taken from 152 patients with rheumatoid arthritis. Information was obtained from 286 of their parents and 451 siblings, a total of 889 individuals Family histories were similarly obtained from 50 patients with rheumatoid spondylitis, 98 of their parents and 196 siblings, a total of 344 individuals or 1233 people in the study series

Family histories were obtained from 242 control patients, their 439 parents and 737 siblings, a total of 1418 individuals in the control series and 2651 individuals in the entire study.

RESULTS

Rheumatoid arthritis occurred in 4 2 per cent of 141 fathers, in 8 3 per cent of 145 [illegible] brothers and in 7.3 per cent of 192 sisters o [illegible] of 5 per cent of relatives [illegible] 10 per cent of the patients with rheumatoid spondylitis [illegible] of their 294 relatives Rheumatoid arthritis occurred in 0 25 per c [illegible] 9 fathers [illegible] 5 per

cent of the 397 mothers, in 1.1 per cent of the 380 brothers and in 0 8 per cent of the 375 sisters of the 242 control families

Rheumatoid spondylitis occurred in 2 per cent of 48 fathers, in none of 50 mothers, in 4 per cent of 76 brothers and in 6 per cent of 61 sisters of spondylitis patients, or in an average of 3 4 per cent of 235 relatives of spondylitis patients Spondylitis occurred in 3 3 per cent of 152 rheumatoid arthritis patients, in none of their 141 fathers or 145 mothers, and in 0 8 per cent of 259 brothers and in 0 5 per cent of 192 sisters Spondylitis was not discovered in any of the control families

In 152 families with rheumatoid arthritis, 120 families had 1 victim, 28 families had 2 victims, 3 families had 3 victims and 1 family had 4 victims The degrees of relationship in families with multiple involvement were father-son 2, brother-brother 2, father-daughter 3, mother-son 7, brother-sister 3, mother-daughter 6, and sister-sister 14

The findings may be summarized by saying that 5 per cent of 738 relatives of patients with rheumatoid arthritis had rheumatoid arthritis compared to 0 1 per cent of 2437 relatives of the controls The disease occurred fifty times as commonly in relatives of patients as in relatives of controls Rheumatoid spondylitis occurred in 3 4 per cent of 235 relatives of patients with this disease compared to 0 005 per cent of 1904 relatives of the control series The disease occurred seventy times as commonly in relatives of patients as in relatives of controls

COMMENTS

No conclusions can be drawn concerning the relationship of rheumatoid arthritis to rheumatoid spondylitis except to say that rheumatoid arthritis was found in 10 per cent of spondylitis patients and in none of their relatives. Rheumatoid spondylitis was found in 3 3 per cent of patients with rheumatoid arthritis and in about 0 7 per cent of their siblings

The overwhelming susceptibility of the relatives of patients with rheumatoid arthritis and rheumatoid spondylitis for the respective diseases is strong evidence pointing to constitutional factors These constitutional factors may be decisive, dividing all members of the population definitely into two mutually exclusive groups In such a case the members of one group would be susceptible to the disease and thus develop it under proper circumstances, the other group would be immune and would never develop the disease under any circumstance We believe such a situation has been proven to exist in the case of gout We suspect it is also true regarding Heberden's nodes The constitutional factor may not be completely decisive but only contributory in the sense that it adds to susceptibility It is not possible with the information at hand to decide which is the case

After the influence of heredity has been established, it remains to discover the pattern of inheritance by study of pedigrees, gene frequency analyses and penetrance It is also desirable to discover the physical basis upon which inheritance depends There is convincing evidence at hand to justify further investigation

THE RELATION BETWEEN RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS, WITH SPECIAL REGARD TO CARDIAC INVOLVEMENT

E. JONSSON, K. BERGLUND, B. EJRUP, O. GÖHLE AND C. E. FRIEDMAN

The question whether rheumatic fever and rheumatoid arthritis are two different types of disease has been much discussed. Clinically, the two conditions differ in many respects, one of the chief differentiating factors being the low incidence of heart involvement in rheumatoid arthritis

In 1941, Baggenstoss and Rosenberg reported that the incidence of heart lesions in their autopsy cases of rheumatoid arthritis was high This extensive study engaged the interest of many observers and led to further investigations which confirmed Baggenstoss and Rosenberg's observations Autopsy cases of rheumatoid arthritis were also studied by two of us (E Jonsson and Kåre Berglund) Among sixty-five autopsy cases of this disease we found heart lesions of a rheumatic type in 36 per cent. In the majority of these cases endocarditis was present. In only a few cases was the myocardium examined histologically

The high percentage of heart lesions found in rheumatoid arthritis at the postmortem led to clinical studies of this disease. Most of the clinical observations, however, are inconsistent with the autopsy findings. They are in agreement rather with the clinical studies made by earlier observers who reported a low incidence of heart findings (Table 20). Only Feiring reported a fairly high percentage of heart involvement (29 per cent) in rheumatoid arthritis. Among his patients there were two with a history of rheumatic fever who manifested heart symptoms, and another two whose past history suggested that they had been suffering from this disease. If these four cases are excluded the incidence of heart involvement in his cases is considerably lower.

Table 20 Incidence of Cardiac Lesions Found in Previous Clinical Heart Studies in Rheumatoid Arthritis

INVESTIGATORS	NUMBER OF CASES	PERCENTAGE OF CARDIAC LESIONS
Bayles, 1943	100	5
Rogen, 1947	33	3
Bishop, Weintraub and Hench, 1947	147	3
Robles Gil, 1948	360	5 5
Rosenberg, 1948	150	3 4

[illegible] between the postmortem and clini-
[illegible]se has not yet been determined At
[illegible]

gative procedures the need for adequate control studies became of paramount importance

CLINICAL MATERIAL

The series here presented (Table 21) comprises thirty-seven cases of rheumatoid arthritis and thirty-seven control cases. The sex distribution was the same in both groups. Also, the age distribution among these cases as well as the average age of the patients of the two groups was practically the same.

Table 21 Description of Present Material

	FEMALE*	MALE*	TOTAL*
Number of cases	26 (26)	11 (11)	37 (37)
Age distribution	30–66 (28–63)	34–58 (36–59)	30–66 (28–63)
Average age	46 (47)	47 (46)	46 (47)

* Controls in parentheses.

Rheumatoid Arthritis Group. The duration of the rheumatoid disease varied between one and twenty years, the average duration of the disease was 7.8 years. The disease was mild in six cases, moderate in twenty-three and severe in eight. All doubtful cases were excluded. In almost all cases the roentgen examination of the joints revealed typical changes. With a few exceptions (see below) the cases were consecutive.

Control Group. All the patients of this group were indoor patients. Their ages corresponded to those included in the rheumatoid arthritis group. Cases with a history of rheumatic affections were excluded. The diseases diagnosed in the control group are shown in Table 22.

Table 22 Diagnoses in the Control Group

DIAGNOSIS	NUMBER OF CASES
Nervous diseases	14
Sciatica	8
Gastritis	8
State after pneumonia	2
Neurosis	1
Mammary carcinoma	1
Colitis	1
Chronic pancreatitis	1
Chronic tonsillitis	1

Excluded Cases. Not included in either group are cases (*a*) with a history of rheumatic fever, (*b*) with a past history suggesting the pre-existence of this disease or (*c*) with other diseases causing secondary heart lesions. Great care was taken to make this selection equal in both groups. Examples of such diseases are hypertension, extensive pulmonary disease, diabetes, hypo- or hyperthyroidism. Cases admitted to the hospital mainly or partly for heart symptoms were not included. This was necessary to avoid overrepresentation of heart disease (see below). If the investigation of a patient revealed a suspected cardiosclerosis the patient was not excluded, it is impossible to exclude arteriosclerosis in a population with this age distribution

ATYPICAL RHEUMATOID ARTHRITIS

CLINICAL FEATURES AND BACTERIOLOGIC STUDIE IN REITER'S SYNDROME

HOWARD J WEINBERGER, LOUIS DIENES AND WALTER BAUER

Though probably recognized and described before 1916, the nongonococcal clinical triad of urethritis, conjunctivitis, and arthritis is commonly referred to as "Reiter's syndrome," after the case described by Hans Reiter in 1916[1] Reiter, believing the disease was caused by a spirochete, introduced the name "spirochetosis arthritica" Spirochetes have not been found by other investigators and the syndrome has since been described as arthritis urethritica (Freund, 1929), as nongonococcal urethritis with conjunctivitis and arthritis (Kristensen, 1930); and as subacute infectious polyarthritis with mucositis (Usseglio and Zancan, 1940). Because of the not infrequent association of diarrhea with the usual triad, it is referred to by some (e g, Berglbock, 1943) as postdysenteric arthritis Conclusive evidence, however, for any specific etiologic agent in this syndrome is still lacking.

The syndrome, though not common, is by no means rare. More than one hundred reports have appeared in the literature, the majority of them since 1941 following the first report in the English literature by Bauer and Engleman[2] The total number of cases observed to date cannot be determined accurately since many do not represent the clinical triad, and in others gonorrhea was not adequately excluded and therefore the cases should not be accepted without question as examples of the syndrome

CLINICAL MATERIAL

We have studied thirty-one patients who presented the clinical triad of urethritis, conjunctivitis, and arthritis Sixteen of these patients were seen during the acute attack and are considered only from the standpoint of their laboratory findings The remaining fifteen patients were observed during the acute attack and were followed for periods up to twelve years All of our patients were males aged twenty to thirty except three who first experienced the full triad at ages thirty-seven, forty-eight, and fifty-two, respectively

ONSET

Though urethritis most commonly heralded the onset of symptoms, many cases appeared to be nonvenereal in origin Four patients denied any venereal contact and eight others could relate no specific exposure to the onset of symptoms Only two of fifteen patients admitted previous gonorrheal infection

Purulent conjunctivitis marked the beginning of the disease in a smaller number of patients Within one to five weeks the entire triad usually had appeared In one instance urethritis and arthritis were present for eight months before conjunctivitis was noted

Constitutional reactions were mild to moderate in severity Weight loss

and fatigue preceded some attacks. Mild, nonbloody diarrhea of one to three days' duration occurred in five of the fifteen patients in addition to the usual triad All of the patients were febrile during the early stages of the attack The temperature ranged between 99° and 101° F, unattended by chills Vasomotor symptoms were present in five patients

COURSE OF THE DISEASE

The duration of the attacks was two to six months Severe articular involvement in two patients persisted for one and one-half years

Ophthalmic Involvement The eye involvement was generally short-lived In addition to conjunctivitis, seen in all the patients, episcleritis was noted in two, superficial punctate keratitis in four, iritis in three and iridocyclitis in one In this last patient the eye involvement was severe and was the predominant feature of the attack Though it persisted for two and one-half months, recovery was complete and without impairment of vision

Genito-urinary Involvement In addition to mucoid or purulent urethritis, prostatitis was noted in thirteen patients Of these, two developed prostatic abscesses which drained spontaneously Six patients also had an acute exudative and hemorrhagic cystitis, characterized by marked dysuria, frequency, suprapubic pain, and so-called abacterial pyuria and hematuria Cystoscopic examination in three patients with cystitis showed intense edema of the bladder mucosa, superficial membranous sloughs and diffuse petechial bleeding The bladder capacity was reduced to 75 cc. in one instance. In two patients the bladder wall edema was sufficiently marked to cause obstruction of the ureters In one patient this led to bilateral hydronephrosis and necessitated a right nephrectomy and a left nephrostomy The genito-urinary involvement persisted for eight months in this case

Seminal vesiculitis was present in two patients In no instance was epididymitis found, in contrast to its not uncommon occurrence in gonorrheal infections

Six of fifteen patients developed circinate ulcerations on the glans penis which became coalescent and were associated with intense edema and inflammation about the glans

Changes in Skin and Mucous Membrane Hyperkeratotic lesions conforming to keratosis blennorrhagica were observed on the soles and palms of two patients, and subungual hyperkeratosis in one. Superficial erosions of the buccal mucosa also occurred

Articular Involvement The articular involvement was almost always the most disabling and persistent feature of the illness, lasting as long as one and one-half years in two patients Nearly always polyarticular (in only one instance monarticular), it most commonly involved the weight-bearing joints The spine was affected in six cases. The arthritis resembled that of an acute infectious arthritis in the suddenness of onset, the tendency to migration and the degree of pain, swelling, heat, and tenderness observed Symmetrical articular involvement occurred in seven patients Mild to moderate residual articular changes were seen in seven patients

Roentgenographic examination of mild cases rarely showed more than slight atrophy In patients with severe articular involvement, diffuse subchondral atrophy with flecky decalcification, similar to that seen in infectious arthritis, was observed This type of alteration was usually reversible. Permanent roentgenologic changes were seen in seven of fifteen patients

These consisted of narrowing and sclerosis about the sacro-iliac joints in four patients, fusion of one toe, subluxation of a wrist, and minor destructive changes in a metacarpophalangeal joint.

Cardiac Involvement. Though there was no clinical evidence of cardiac involvement, four of eight patients on whom electrocardiograms were taken showed abnormalities consisting of serial T wave changes, deep Q_3, prolonged auriculoventricular conduction, and persistent right bundle branch block in one patient each.

LABORATORY STUDIES

Chemical and cytologic studies done on forty-five synovial fluids from fifteen patients showed alterations consistent with those seen in mild cases of both infectious arthritis and rheumatoid arthritis. The fluid was cloudy and clotted readily. The leukocyte count ranged from 2,900 to 52,800 per cubic millimeter, with an average of 66 per cent polymorphonuclear cells. The sugar was reduced in thirteen of twenty-three fluids. The average serum-synovial fluid glucose difference was 16 mg per cent. Mucin was lowered and precipitated only fairly. The protein content was uniformly elevated. The intensity of the inflammatory response usually paralleled the clinical course. Lowering of the leukocyte count, improvement in the character of the mucin, and a rise in fluid sugar in serial determinations have indicated subsidence of the inflammatory process before this was apparent clinically.

Biopsy specimens of synovial tissues were obtained from six knee joints after periods of involvement varying from four days to three months. All specimens showed acute and chronic inflammatory changes, similar in the reaction pattern, irrespective of the duration of involvement. The acute changes were chiefly exudative, characterized by congestion accompanied by small hemorrhages, edema and polymorphonuclear infiltration.

The chronic inflammatory changes consisted of lymphocytic infiltration tending to be perivascular (more pronounced in the superficial portion of the synovia), hypertrophy and hyperplasia of synovial cells and proliferation of fixed connective tissue cells and blood vessels. The general reaction pattern differs somewhat from the classic descriptions of both rheumatoid and pyogenic synovitis though the histopathology of specimens of comparable durations has not been established clearly.

Routine laboratory studies showed a mild to moderate leukocytosis, elevation of the sedimentation rate, and pyuria. Detailed bacteriologic studies were undertaken to identify an etiologic agent. Routine and special cultural media were employed for both aerobic and anaerobic growth. Serologic tests for gonorrhea, undulant fever, and bacillary dysentery were negative.

Dark field examinations and Frei tests were negative, as were examinations for inclusion bodies. Mice and monkeys inoculated with urine, prostatic secretions, urethral, conjunctival and synovial membrane scrapings and joint fluid showed no abnormalities. Similar material was inoculated into embryonated eggs without evidence of bacterial or virus growth.

The only suggestive evidence obtained thus far concerning the etiology of this syndrome has been the finding of pleuropneumonia-like organisms in the synovial fluids of two patients and in the genito-urinary tracts of twelve patients. It will not be possible to evaluate fully the significance of these observations until more is known of the nature and origin of these forms.

There is good evidence that pleuropneumonia-like organisms may be unusual growth forms of ordinary bacteria. Such forms appear more frequently with the use of penicillin clinically or its incorporation in culture media. There is evidence also that these forms may occur normally in the genitourinary tract of both males and females.

FOLLOW-UP

The clinical course of fifteen patients was observed for an average period of four and one-half years. Five patients had a single attack with apparent complete recovery. Ten had recurrent attacks of what presumably was the same illness, involving one or two of three systems in five patients and all three systems in the remainder Those with recurrent attacks have been separated into two groups. One is illustrated by a patient who had a characteristic onset of the triad in 1940 and seven recurrent acute episodes up to 1949, with ocular and articular involvement alone on two occasions. The other group is illustrated by a patient who had repeated episodes involving one or two of the three systems for many years and then finally showed involvement of the three systems simultaneously, thus fulfilling the criteria for the diagnosis of Reiter's syndrome It seems likely that the previous attacks were part of the same illness

Patients have been treated with sulfonamides, penicillin, streptomycin, and aureomycin. These agents have not definitely influenced the course of the acute attack.

COMMENT

Despite extensive bacteriologic investigation the etiology of the syndrome is still unknown Gonorrhea simultaneously involves these three systems and therefore always should be ruled out. In view of the negative smears, cultures, and serologic tests for gonorrhea observed in our cases and those reported in the literature, it is very unlikely that the gonococcus is responsible for the syndrome.

Rheumatoid arthritis with pustular psoriasis involving the skin and mucous membranes possibly could produce an entirely similar picture. Indeed, some of the cases followed for a prolonged period do bear resemblances to rheumatoid arthritis Exacerbations and remissions occur without the characteristic triad and the articular involvement may be symmetric. Residual changes have resulted in patients who had repeated attacks Iritis and vasomotor findings also were observed However, there are striking differences between rheumatoid arthritis and Reiter's syndrome These include (*a*) the unusual onset with the triad of systems involved, (*b*) the acute character of the articular involvement resembling infectious arthritis, (*c*) the excellent prognosis for initial attacks of arthritis; (*d*) the contrasting histopathology between Reiter's and the usual rheumatoid pathologic specimens; (*e*) the absence of subcutaneous nodules; (*f*) the rarely observed family history of rheumatoid arthritis, and (*g*) the tendency for the roent-

mucous mem-
articular in-

volvement of relatively chronic and progressive nature This may possibly be the role of pleuropneumonia-like organisms On the basis of our experience to date, we adhere to the concept that Reiter's syndrome is probably separate from rheumatoid arthritis and is presumably infectious in origin

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THE STATUS OF THE TWO TYPES OF ARTHRITIS FOLLOWING GONORRHEA

With a Report of Eighty-nine Cases Resembling Rheumatoid Arthritis

VICTOR G. BALBONI AND DAVID M KYDD

Arthritis is one of the well recognized and dreaded complications of gonococcal infections, and was reported as occurring in roughly 2 to 5

therapy

PATHOGENESIS OF METASTATIC GONORRHEAL ARTHRITIS

In true gonorrheal arthritis there is a metastatic infection of the articular tissues[1-4] Its onset is usually explosive, preceded by a chill and accompanied by fever. At first, the process may be a migratory polyarthritis, but shortly it localizes in one or rarely more joints which become acutely swollen and inflamed Tenosynovitis may occur about affected joints, especially when the small joints of the hands and feet are involved Symmetric joints are usually not involved. The joint fluid contains a high cell count with a preponderance of polymorphonuclear leukocytes, gonococci may often be recovered from the joint fluid by bacteriologic techniques and less commonly by smear, the sugar content of the synovial fluid is usually decreased and the protein content is increased Untreated, this type of arthritis tends to progress to destruction of the articular cartilage and to fibrous ankylosis of the joint, but it does not become chronic and there is no tendency for new joints to be progressively involved If treated early, it responds dramatically to adequate intramuscular penicillin therapy with complete arrest of the infection[3-6] Intra-articular penicillin therapy is usually not necessary, since it has been shown that penicillin penetrates readily into joint fluid following its intramuscular administration[7] Articular tissues possess limited potentialities to repair themselves The degree of residual joint damage is proportional to the virulence of the infecting gonococci, the resistance of the host, and the duration of time the joint infection remains untreated However, the virulence of the infecting gonococci and the resistance of the host's tissues are of less importance in determining the residual joint damage than is the speed with which penicillin therapy is instituted Gonococci are among the more penicillin-sensitive bacteria, and to our knowledge no naturally occurring gonococci have been shown to be completely penicillin resistant both in vivo and in vitro

PATHOGENESIS OF CHRONIC GONORRHEAL ARTHRITIS

The pathogenesis of the second and now more common type of arthritis following gonorrhea is poorly understood. It may begin as may the first type with a migratory polyarthritis but differs in that the onset tends to be less acute and is not apt to be preceded by a chill. Fever may or may not be present but is seldom high. Symmetric joints are often affected. The clinical course tends to be chronic and progressive involvement of new *joints is the rule. Gonococci are never obtained from the joint fluid*, which has a variable cell count with a tendency to be lower in total and polymorphonuclear leukocyte counts than in the metastatic type. The sugar content of the synovial fluid is usually not abnormal. Penicillin therapy, though eliminating the urethral infection, does not appreciably alter the course of this arthritis.

CLINICAL STUDY OF CHRONIC GONORRHEAL ARTHRITIS

At Ashburn General Hospital, one of the Army's war-time centers for the treatment of arthritis, we had the opportunity to observe eighty-nine cases of this chronic type of arthritis following gonorrhea. The arthritis in all eighty-nine cases involved peripheral joints, although in some cases arthritis of the spine was also present. The patients were all males of military age whose urethritis was contracted and arthritis developed in the various areas of military operation. The diagnosis of gonorrheal urethritis was *based in* [illegible]

in the urethral discharge. In some cases the diagnoses were further supported by positive gonococcus cultures from the urethra or urinary sediment.

Time of Onset. In the majority of cases (sixty-eight) the arthritis set in [illegible] in nine cases it set in [illegible] after more [illegible] to one or [illegible] involved [illegible] cessary to [illegible] nts some-*times became* involved by the arthritis while the patient was receiving penicillin.

When we first started seeing these cases and before we were familiar with the clinical picture it was our policy to administer large doses of [illegible]

the patients with a history of previous arthritis had valvular heart disease. Thirty-two patients had had rheumatoid arthritis and thirteen other patients had had a previous arthritis following a previous gonorrheal infection In 95 per cent of the cases studied the arthritis was polyarticular and symmetric joints were involved in more than 50 per cent of the cases.

Sixteen of these eighty-nine cases, in addition to having arthritis of the peripheral joints which precipitated their hospital entry, had evidence by history and roentgenography of a pre-existing rheumatoid spondylitis. From the nature of the roentgenographic changes it was felt that this spondylitis in all sixteen cases had existed for a number of years These cases were of special interest because of the high familial incidence of rheumatoid arthritis (31 per cent) and the frequency of previous attacks of arthritis, both spontaneous (50 per cent of the cases) and following previous gonorrhea (31 per cent).

Nature of Onset The onset in most cases was insidious, and in only four cases was the onset preceded by chill Low grade fever was not uncommon during the course of the arthritis, but in only 15 per cent was this febrile response 101° F or more In no case was the febrile response favorably affected by penicillin therapy In a few cases sulfonamide therapy was also given without effect on the temperature. In more than half of the cases the leukocyte count in the blood was within normal limits at the onset of the arthritis In those cases in which it was elevated the counts averaged around 12,700 cells Differential counts showed the polymorphonuclear leukocytes to be only slightly increased Joint fluid studies revealed a sterile fluid with a mild to moderate pleocytosis averaging about 10,000 cells with 74 per cent polymorphonuclear leukocytes Results of quantitative sugar determinations were within normal limits in all cases in which this factor was tested Thinning of the subchondral bones as evidenced by roentgenographic studies developed in one or more of the affected joints in sixty-two of the cases The sedimentation rate was elevated in all but two cases

Results of Treatment All of the eighty-nine cases in this study received a trial on penicillin therapy in addition to that necessary to cure their urethritis However, as soon as it was determined that the penicillin was not affecting the arthritis they were placed on the conservative therapeutic program similar to that used on our other rheumatoid patients This included bed rest for varying periods, the control of pain with salicylates, a [illegible]

essentially asymptomatic with normal sedimentation rates and normal-appearing and functioning joints By "essentially asymptomatic" we mean that the patients did not complain of painful joints or constitutional symptoms Many, however, did continue to experience mild stiffness of the affected joints after rest, as well as arthralgias with changes in weather and following exercise Thirty per cent remained mildly active but no longer required hospital care, and 10 per cent were transferred for more prolonged hospital care because of persisting, moderately severe activity of the joint disease While under observation, only six cases went on to develop permanent peripheral joint damage as evidenced roentgenographically by narrowing of the joint space

COMMENT

Even before the advent of penicillin therapy it was generally recognized that arthritis following gonorrhea could be divided into two rough types In the first type, or what we term as "true" or "metastatic gonorrheal arthritis," the arthritis was a moderately acute disease that was self-limited regardless of the type of therapy given It burned itself out within a few months and did not tend to become chronic. The second type of arthritis following gonorrhea tended to be more chronic and resistant to therapy. Many observers, however, have felt that the pathogenesis in all cases was essentially the same, namely, that gonococci invaded the joint space or periarticular tissues.[2, 8–10] If many virulent organisms invaded the joint, a purulent arthritis ensued, while if the organsims were few or attenuated, the arthritis presented a sterile fluid with low cell count. Keefer[1] and Spink found high antibody titers in the joint fluids in this latter type of case and believed this explained the failure to demonstrate gonococci; in cases where *gonococci could be demonstrated, no antibodies were present in the fluid* Some authors, however,[3, 11–13] have felt that this chronic type of arthritis following gonorrhea was rheumatoid arthritis, the gonorrhea acting as a trigger mechanism to set off the rheumatoid process in a susceptible individual Hench has emphasized this point of view in recent articles and states, "Acute gonorrhea can provoke the first appearance of rheumatoid arthritis, reactivate previously active but currently quiescent rheumatoid arthritis, or aggravate notably a coexistent rheumatoid arthritis."[3, 4]

Examination of the synovial fluid in this chronic type of arthritis following gonorrhea reveals little to suggest that bacteria are in the joint fluid or neighboring tissues. This impression is confirmed by the complete failure of the arthritis to respond to penicillin therapy and the not infrequent involvement of new joints while on penicillin therapy. Gonococci are among the more penicillin-sensitive bacteria,[10] and in no case in this series did the urethral infection fail to respond to one or more courses of penicillin.

An examination of the family and past histories of these patients reveals an arthritic diathesis *The family incidence of arthritis is 16 per cent,* and the past histories reveal previous arthritis in 51 per cent. Our figures on a comparable group of patients with acute rheumatoid arthritis not associated with gonorrhea are about the same, with a family incidence of 15 per cent and a past history of joint disease in 36 per cent. The polyarticular nature of the disease with a tendency to involvement of symmetric joints, the joint fluid findings, and the clinical course all simulate rheumatoid arthritis. Rheumatoid arthritis is commonly referred to as a chronic deforming arthritis and it may be argued that the fact that 60 per cent of our cases [illegible] rvation period [illegible] [14] has pointed [illegible] *e or subacute* recurrent disease with a tendency toward remissions with little or no detectable joint damage following the first few attacks. Our total improvement rate of 90 per cent compares favorably with that reported by Short and Bauer[15] of 81 per cent improvement in a series of rheumatoid subjects in whom the duration of the disease was six months or less at the onset of therapy. The sixteen cases in our series who had roentgenographic evidence of an old rheumatoid spondylitis and who developed acute periph-

eral joint affections following gonorrhea further emphasize the relationship between gonorrheal infections and rheumatoid arthritis. In these cases the existing rheumatoid arthritis of the spine was presumably aggravated by the gonorrheal infection, with consequent spread of the rheumatoid process to the peripheral joints.

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RHEUMATOID SPONDYLITIS

THE NATURAL COURSE OF ANKYLOSING (MARIE-STRÜMPELL) SPONDYLITIS AND ITS RESPONSE TO TREATMENT*

DONALD C. GRAHAM, A A FLETCHER AND WALLACE GRAHAM

In a study of 150 patients with ankylosing spondylitis of two to thirty-three years' duration, a complete history was obtained and detailed clinical, hematologic and radiologic examinations were carried out on each case by one observer The course of the disease prior to the institution of active therapy was studied and an attempt was made to assess the influence of treatment upon this course

A striking characteristic of ankylosing spondylitis, emphasized by this survey, was its marked variability It became clear that there is no predestined course and no predictable outcome in any individual case

NATURE OF ONSET

The feature of inconsistency became apparent from the onset of the disease In 35 per cent of cases the onset was acute and of sufficient severity to require cessation of duties In the remaining 65 per cent, it was insidious

In over half the cases the onset was unrelated to any precipitating circumstance Twenty-three per cent developed their first symptoms following exposure to cold, damp and fatigue In 12 per cent of the patients the initial symptoms developed in relation to an acute infection It was striking that two-thirds of the infections associated with the onset of spondylitis were caused by the gonococcus

In 70 per cent, initial symptoms involved the low back area Early involvement of the low back with subsequent upward spread was the usual course of the spinal component of the disease In 14 per cent, the disease began in peripheral joints but at some time during the course of their illness, 30 per cent of the patients showed objective peripheral joint lesions indistinguishable from those of rheumatoid arthritis Complete resolution in the peripheral joints was the result in over half the cases with such involvement, only 13 per cent showing chronic residual peripheral joint disease This is strikingly different from the course of rheumatoid arthritis In 9 per cent, the disease began with an attack of pain of sciatic distribution

COURSE OF THE DISEASE

Like its modes of onset, the subsequent courses followed by the disease

frequency, severity and duration The earlier complete remissions became

* This study was financed through a Canadian Red Cross fellowship

replaced by persistent discomfort, still subject to flare-ups. The tempo of this advance varied greatly as did the resulting disability.

Another group, constituting 20 per cent of the cases, had a mild gradual ns no a course for thirty years.

A further 5 per cent of the cases showed a prolonged mild course as just described, but late in their disease an accentuation of its activity occurred, leading to

Ten per t course fror t invalidism. sionally occurred despite intensive therapy

In another 10 per cent the disease began as an acute arthritis in multiple peripheral joints Over a variable period the peripheral joint lesions usually subsided, but not always completely. As the peripheral lesions regressed, symptoms referable to the spine developed and progressed, with exacerbations and remissions, to a variable degree of disability.

In 5 per cent of the cases the onset was characterized by an acute, severe attack of back pain. This was gradually succeeded by a mild course with minor flare-up the disease.

A common progresses to complete spinal ankylos was rarely borne out in this series The degree of ankylosis and rapidity of its development are unpredictable A rigid "bamboo spine" was noted relatively soon after the onset in some cases, while in others a surprising degree of mobility was maintained as long as thirty-three years after the disease had begun. At any stage during its course, ankylosing spondylitis may subside spontaneously leaving little disability. Such spontaneous arrest is rare and, as a rule, of limited duration, but in a few cases may be prolonged or even permanent.

TECHNIC OF ROENTGEN ADMINISTRATION

was administered, the roentgens at 10 milli- ough 0 25 mm copper, were administered on successive days to each of five portals covering the cervical, dorsal and lumbar spine and each sacro-iliac area. The portal size was approximately 10 x 20 cm These five exposures constituted one course of therapy. Courses were repeated at intervals of one month The number of courses administered varied according to the apparent response to such treatment. The majority of patients received at least three, and in several cases as many as six such courses were given

RESULTS OF TREATMENT

For purposes of assessing the results of treatment, the patients have been considered in four groups.

Group I comprised 33 cases (22 per cent of the series) and consisted of those who had received only sporadic symptomatic treatment. The majority had mild, nondisabling, yet typical disease showing no tendency to advance. A small number of cases in group I had more severe disability but

had carried on at their work against advice and continued to progress unfavorably. The number of cases which remain mild, with little disability, in the absence of any active treatment, is impressive.

Group II consisted of five patients still under treatment and not suitable for assessment.

Group III comprised 58 patients (39 per cent of the series) who had been treated in hospital but had never received roentgen therapy These veterans were afforded a unique opportunity to avail themslves of prolonged hospital treatment in an arthritis center, free from many of the financial encumbrances of the civilian The program of therapy centered about the basic principles of rest, protection from deleterious influences, maintenance and improvement of functions already affected and prevention of such sequelae as deformities and contractures. Daily group exercises, postural training and educational measures were supplemented by suitable physiotherapy and analgesics The majority reported subjective relief from a fracture board and a considerable number benefited from spinal supports However, such spinal supports did not invariably prevent the development of deformities The duration of hospitalization varied from three months to over two years depending on the progress of the individual case. It was estimated that 60 per cent of the cases treated in hospital by the measures just discussed, manifested some degree of benefit as judged by decrease in pain and fatigue, increase in mobility, relief of muscle spasm, decrease in sedimentation rate and gain in weight Ninety per cent of the patients in this group were considered fit for some form of employment at the time of this survey and nearly all of these were actually working

Group IV consisted of fifty-four patients (36 per cent of the series) who had completed a period of deep roentgen therapy This group included thirty patients who had failed to respond to a previous period of treatment in hospital It is also of some note that the degree of disability before treatment was begun was considered to be somewhat greater in group IV, the roentgen-treated cases

Despite a relatively brief follow-up period of one month to four years after completion of treatment, it became evident that the results of roentgen therapy were not uniformly impressive. Fifty-eight per cent of those so treated derived some degree of benefit. Forty-two per cent noted no improvement Half of the patients who did not benefit showed no significant change in their disease The other half continued to progress unfavorably.

In all of the 58 per cent who improved with roentgen therapy, subjective benefit was claimed, varying in degree from a slight but definite decrease in severity of symptoms to complete symptomatic relief. In the majority, the symptomatic remissions were incomplete, some complaints persisting but to an appreciably milder degree than before treatment Thirteen per cent exhibited objective improvement in the form of increased spinal mobility and chest expansion, disappearance of muscle spasm and improved general nutrition One patient with moderately severe active spondylitis manifested complete subjective and objective remission which was maintained throughout a fifteen-month follow-up period In 7 per cent of the roentgen-treated cases the disease progressed objectively despite symptomatic relief. Twenty-two per cent of those given roentgen therapy showed a significant sustained drop in sedimentation rate. Fifty-three per cent showed no significant change, and in 9 per cent the sedimentation rate rose

during therapy and remained above the pretreatment level The records of 16 per cent of the cases were inadequate for determining the effect of roentgen therapy on the sedimentation rate.

At the time of this survey, approximately 90 per cent of the patients treated by roentgen therapy were considered employable.

There were no satisfactory criteria for selecting patients who might be expected to benefit from roentgen therapy. Neither the severity nor the duration of the disease were of any value in this regard Actually, three of the four patients with spondylitis of over twenty years' duration derived appreciable symptomatic relief.

Untoward Effects of Roentgen Therapy Serious complications of this form of treatment were rare and were confined to hematopoietic damage Leukopenia, lymphopenia, and transient eosinophilia were common, but in nearly all cases the hematopoietic tissues regenerated to a normal state. Of the patients treated by roentgen therapy, 48 per cent developed leukopenia (leukocyte count less than 5000 per cu. mm.), 19 per cent developed lymphopenia (lymphocytes less than 1000 per cu mm), and 15 per cent developed transient eosinophilia (eosinophils in excess of 400 per cu mm). No cases of radiation anemia or thrombopenia were encountered In one patient, however, serious hematopoietic injury appeared during the sixth course of treatment after a total dosage of 6,600 roentgens. This was followed by unrestrained myeloid hyperplasia culminating in acute myeloid leukemia The patient died seven weeks after the earliest changes in the peripheral blood had been noted Persistent amenorrhea developed in the only woman given roentgen therapy Radiation sickness was common (77 per cent of patients treated) but rarely of sufficient severity to require cessation of treatment

COMMENT

Comparative assessment of the value of therapeutic measures is difficult and complicated The inherent unpredictability of the course of the disease renders the effect of any treatment difficult to evaluate The same factor makes it impossible to obtain two groups of cases that one can be sure are comparable before therapy Because of the chronic, long-drawn-out course of the disease, any interpretation of the value of therapy based on a short-term period of observation might well be fallacious Favorable results of roentgen therapy are based on the patients' own claims in most instances It has already been stressed that over half the patients in this series who were given deep roentgen therapy had failed to benefit significantly from a previous period of hospital treatment

In view of these considerations, a comparison of the relative value of hospital treatment alone and of roentgen therapy, based on a statistical examination of these therapeutic results, would be of questionable validity

However, the following conclusions appear justified Neither roentgen therapy, nor the hospital program previously outlined, cure spondylitis There is no evidence that roentgen therapy arrests the disease in an appreciable number of cases. About 40 per cent of the patients treated with roentgen therapy derived no apparent benefit Serious complications of such treatment are rare but do occur

On the other hand, roentgen therapy did afford some degree of subjective relief to about 60 per cent of the patients so treated, many of whom

had failed to respond to a prolonged trial of other measures This in itself appears a worthwhile accomplishment In a small number of cases, the benefit from roentgen therapy was striking

In view of these observations, and the fact that there are no criteria for excluding cases not likely to respond favorably, it seems justifiable to continue to employ roentgen therapy as an added physical means of affording symptomatic relief, but only as an adjunct to other general measures.

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SYNTHETIC ESTROGENS IN THE TREATMENT OF ANKYLOSING SPONDYLITIS

F COSTE AND S BONFILS

Treatment of ankylosing spondylitis with synthetic estrogens has seemed logical because of (1) the predominance of the disease in the male sex and the augmentation of excretion recently observed for 17-ketosteroids, (2) the effects of estrogens on the ligaments of the pelvic articulations, especially the sacro-iliac, and (3) the recalcifying action of estrogens on osteoporotic bone.

Early trials by ourselves and others (e g, Freyberg in 1942) were disappointing However, remarkable improvements were noted later when we used larger doses, and our favorable results with synthetic estrogens in treating ankylosing spondylitis, reported in 1946 and 1947, have been confirmed by some other French investigators

SUMMARY OF RESULTS

In the present study, twenty-five men with ankylosing spondylitis were treated with synthetic estrogens Sixteen of these patients obtained definite and lasting improvement, six were not improved and three became worse or were intolerant to the drug Of the sixteen improved, ten experienced reduction in both stiffness and pain (in some cases sufficient to permit an active life), the other six improved only by reduction or disappearance of pain

Among the improved patients, nine showed a substantial reduction in blood sedimentation rate within three weeks to two months, five showed no change, and one patient had an increased sedimentation rate, the rate for one improved patient was not measured Among the unimproved patients, the sedimentation rate remained unchanged in five and increased in four

The relief afforded patients who were improved by estrogen therapy was protracted, especially when the estrogens were implanted as pellets Two such patients, recently seen, have not suffered any pain for six and eight months, respectively

ASSESSMENT OF RESULTS

The degree of improvement, as far as pain is concerned, can be reported subjectively by the patient Reduction in stiffness, however, should be evaluated objectively by measuring height, chest size, movement in waist articulations, distance from the spine of the seventh cervical vertebra and the posterior line of the skull to the posterior vertebral plane,

and distance between the chin and the sternal manubrium, with the head in forced flexion and forced extension These measurements permit assessment of the dorsal kyphosis. In addition, periodic standing profile photographs are useful for judging deformities of the spine.

DRUGS USED

Diethylstilbestrol was most often used and was active in a rather high proportion of the cases. Because the large doses frequently resulted in digestive disturbances if given by mouth, it was usually administered first in daily intramuscular injections of 20 mg or more. If no intolerance was demonstrated after fifteen days, a dose of 300 mg. was implanted and renewed at intervals of six to twelve months. If diethylstilbestrol was not tolerated, daily doses of 10 mg of 7-methylbisdehydrodoisynolic acid were administered in fifteen-day courses, repeated after two to three weeks, or 300 mg of the latter drug was implanted and periodically renewed.

Based on the results of a previous study of the effects of synthetic estrogens on menopausal pains and on arthroses, we classify these substances in the following order of decreasing activity: diethylstilbestrol, 7-methylbisdehydrodoisynolic acid, dienestrol, derivatives of 6-hydroxy-2-naphthalenepropionic acid (allenolic acid), hexestrol.

EFFECTS OF VARIOUS FACTORS ON RESULTS

A sufficiently large dose was found to be essential for therapeutic results

[illegible] manifestly insufficient implanta-

ation.

affect the results

of treatment with dosages of the quantity used in this study. These variables included the following chemical composition of the drug, method of administration (oral, intramuscular injection, or implantation, and implantation of 300 mg of the drug "compensated" by the addition of 100 mg of testosterone in an attempt to palliate feminization effects); time since onset; extent of involvement; age of patient; etiologic factors; nature of response to previous treatment, and stage of the disease (active, with acute pains, versus chronic)

UNTOWARD EFFECTS

Except for a few cases in which the patient was intolerant to the drug, the only undesirable results of the treatment were feminization effects These consisted of, first, painful swelling of the breasts and pigmentation

[illegible]

occurred between the eighth and fifteenth days [illegible]

tion of the drug, but as much as one month following implantation Only three patients experienced no feminization effects, and none of these three benefited from the treatment Most of the patients regarded these manifestations as minor inconveniences in the light of the improvement in their disease.

Attempts to prevent these effects by the implantation of 100 mg. of testosterone with 30[illegible]

tion of testosterone,

might have been eff[illegible]

ing the therapeutic effects of the synthetic estrogen

REFLEX DYSTROPHY

REFLEX DYSTROPHY IN THE EXTREMITIES

OTTO STEINBROCKER AND LYON LAPIN

Reflex dystrophy in the extremities is a localized disturbance characterized chiefly by pain of varying degree, vasomotor disorders, disability, swelling, trophic changes of soft tissues, usually spotty osteoporosis and a number of lesser signs in an affected limb Some or all of these features may be present These disorders have been reported to occur in the face and spine as well as in the extremities We are concerned here only with involvement of the limbs These reflex phenomena and changes in a limb obviously simulate many varieties of arthritis and musculoskeletal disease for which they may be treated ineffectively They may be superimposed, we have found, on infectious arthritis, gout and bursitis to produce a bizarre clinical picture unresponsive to measures for the original condition We identified six cases over a period of several years, but in the past two and one-half years, since we have been looking for them, we have studied almost 100 cases

The symptoms of reflex dystrophy usually are prolonged and may resolve completely, spontaneously or therapeutically, or they may prove partly reversible or irreversible They are presumed to arise from reflex stimulation of the autonomic, mainly the sympathetic, and somatic nerve supply to the affected part, sustained by a continuous bombardment of the spinal cord by stimuli from the primary lesion and peripheral foci of irritation set up by it. The interpretation of the underlying mechanism in these disorders largely represents a clinical deduction supported by empiric and experimental observations, but much still remains to be explained. These reflex features evidently are provoked by a variety of causes. They may develop as an aftermath, usually as a complication, of some primary process, medical or surgical, but in many cases their severity may overshadow the causative condition in diagnostic and therapeutic importance

For many years a variety of seemingly unrelated clinical disorders have been described in the surgical and medical literature as separate entities, but they present the features now regarded as characteristic of the symptom-complex termed reflex dystrophy These conditions include causalgia, Sudeck's atrophy, post-traumatic osteoporosis, painful disability of the shoulder following coronary occlusion, 'post-infarctional sclerodactylia," palmar and digital contractures, the swollen atrophic hand associated with cervical osteoarthritis, certain changes in the involved limbs of hemiplegics, and a number of others Increasing evidence indicates that, although the etiology of these variously designated syndromes may be different, many of their clinical characteristics and probably the neurophysiologic mechanisms underlying their development are very similar, if not identical Favorable response to diagnostic and therapeutic sympathetic block in conditions with various causes occurs frequently enough to strengthen this concept

CLINICAL MATERIAL

Our report is based on a study of seventy-two consecutive cases of reflex dystrophy of the limbs, sixty-four in the upper extremities and eight in th

lower Not only has the upper extremity been affected more frequently in

periods of from several months to over ten years. In this series there was a great diversity of causes, chiefly medical. In some cases none could be demonstrated Symptoms and signs of reflex dystrophy may present all degrees of severity, from minor complaints in only one digit to major involvement of a limb. Even in the most severe clinical picture of reflex dystrophy, such as the shoulder-hand syndrome, certain typical symptoms may be absent Nearly all of our patients, however, showed extensive signs and the clinical picture evolved from acute to chronic states

COURSE

We found it possible in the majority of cases to divide the course of the fully developed clinical picture into three stages or phases. Phase 1 consisted mainly of localized pain, vasomotor disturbance, disability of the limb, and often swelling of the hand or foot with spotty or ground-glass osteoporosis shown in the roentgenograms Phase 2 was characterized by resolution of signs and symptoms, with osteoporosis especially noticeable In phase 3 trophic alterations and contractures were the striking findings The duration of the earlier stages averaged three to six months, but in individual cases the time factors and the extent of involvement were irregular Sometimes a rapid progression to the final changes may occur.

A distinguishing feature of the majority of cases in the early stages is the localized autonomic or sympathetic disturbance reflected by changes in the skin temperatures, oscillometric readings and blood flow gradients. So far we have not found consistent chemical differences in venous blood of the affected and unaffected limb, or in the cellular elements of blood from symmetrical finger tips Skin and muscle biopsies in two of our patients revealed no characteristic changes

PROGNOSIS

The subject of reflex dystrophy may be clarified, we believe, by regarding the variable clinical features and courses as expressions of the different degrees of reflex physiologic reactions, neurovascular and motor, to provocative internal or external agents For satisfactory diagnosis, prognosis and therapy it seems important to distinguish incomplete or abortive forms, as well as the severe and typical ones, at an early stage, at least before phase 3 To guide prognosis and treatment the terminal stage obviously must be recognized The outcome in any case, spontaneous or therapeutic, must depend on the extent of involvement and on the underlying cause. There is a prevalent impression that these disorders naturally disappear in due time As a matter of record, in 30 to 60 per cent of some series with various degrees of reflex dystrophy of traumatic origin, spontaneous partial or complete resolution, sooner or later, has been reported. In many patients this disorder evidently may be influenced by treatment with, or without, residual alterations However, disabling irreversible changes of two to ten years' duration so far, probably permanent, occurred in approximately 10 per cent of our cases with involvement of the upper extremity. (These patients were not treated by interruption of the sympathetic supply.) In spite of opti-

mistic references in the literature to the outcome of these conditions, our experience emphasizes that long-standing and probably permanent changes or disability may be an unpredictable possibility in any case, unless effective therapy is initiated early.

TREATMENT

Among our patients, sympathetic block gave complete resolution of symptoms in 29 per cent of cases and appreciable symptomatic relief in another 58 per cent in the upper extremity Results in the limited number with involvement of the lower limb were excellent (75 to 100 per cent recovery) after one or two blocks

The exact contribution, or the superiority, of different therapeutic approaches to these variable clinical disorders ultimately will be clarified by observations on untreated control groups and the comparative results of the many methods of treatment advocated Therapeutic deductions in such an irregular clinical picture with a respectable frequency of natural recovery require extensive, well-controlled observation and follow-up The prospect for development of a generally effective and dependable oral or parenteral agent for reflex dystrophy in the near future is very promising, but it does not seem to have been accomplished in our experience so far with the substances now available At present, interruption of the cervicothoracic or lumbar sympathetic ganglion by nerve block, and surgery in selected cases, seem to be the most rapidly useful therapeutic methods in the greatest number, whatever the cause The earlier the stage the better the prospects of symptomatic response Whether the frequency of irreversible changes is materially influenced we cannot state with certainty as yet, although our results and those of others make it likely Such treatment is usefully supplemented by physiotherapeutic and rehabilitative measures to prevent further disability and to overcome the limitations of function already present

DISCUSSION

JONAS HENRIK KELLGREN

The cases of painful shoulder following coronary occlusion and other distant lesions certainly suggest a reflex mechanism, but is it really as simple as this delightful story of the vicious circle and the central excitatory state of the internuncial pool?

My own experience is surgical and so I have a rather different slant on this problem In classical cases of causalgia, with typical reflex spasms of pain, sympathectomy gives dramatic and permanent relief, but these cases are extremely rare in civil life and we were only able to find seven such cases among nearly 2000 peripheral nerve lesions treated at the Oxford center A more common cause of pain following trauma is deep hyperalgesia with cold pain In these cases sympathectomy may give partial relief by abolishing reflex vasoconstriction and so interfering with the normal cooling of the part The commonest cause of pain in nerve injuries is undoubtedly the exaggerated and explosive sensory response to stimulation which always occurs during regeneration but which may sometimes be

very pronounced But this condition of hyperpathia is unaffected by sympathectomy.

We have recently been studying the effect of short periods of arterial occlusion in various painful states, and we find that inflammatory conditions give a dramatic build-up of pain during circulatory arrest; conversely, a slight increase of the local circulation may give equally dramatic relief and this is another mechanism by which sympathetic block can relieve pain

Although the theory of the vicious circle as a cause of pain remains unproven, it is nevertheless certain that sympathetic block can relieve pain in a variety of conditions. The difficulty is in selecting suitable cases, and for this we need more concrete evidence about the various mechanisms by which sympathectomy relieves pain. Even with our present knowledge sympathetic block may be a most valuable form of therapy, particularly in helping to tide patients over an acute painful episode, and I am sure this procedure should be used more frequently.

* * *

REFLEX SYMPATHETIC DYSTROPHY

JONAS HENRIK KELLGREN

We have studied this problem intensively in cooperation with Professor A. M Boyd's Neurovascular Unit. The concept of reflex sympathetic dystrophy apparently rests upon the observation that a sympathectomy sometimes relieves pain, but most critical observers have been struck by the temporary and rather unpredictable nature of this relief, and I suspect that we do not really know what we are doing when we submit a given patient to sympathectomy The most dramatic and permanent relief is undoubtedly obtained in cases of true causalgia, in which a nerve injury is accompanied by the classic reflex spasms of pain, but these cases are extremely rare in civilian life.

By far the commonest condition is the syndrome we have described as *deep hyperalgesia with cold pain This is found in a variety of nerve* injuries, glomus tumors, fractures and other painful states of the extremities in which the deep pain nerves are for some reason abnormally sensitive, and therefore give rise to excessive pain during cooling In these cases sy[illegible] ...striction and so int[illegible]

the affected extremity is cold and blue, but there are also many people with cold blue extremities who suffer no pain at all, and it is only when vasoconstriction is combined with deep hyperalgesia that it contributes to the painful syndrome of which the deep hyperalgesia is the essential cause

The third group of cases are *those in which a minor trauma is* followed by a severe localized rheumatoid arthritis with intense osteoporosis. This occurs most commonly in the carpus and tarsus These cases are commonly labelled Sudeck's atrophy, but I have never seen a case of Sudeck's atrophy that could not more reasonably be classified as local rheumatoid arthritis Professor Boyd has done sympathectomies on two patients of this type but

although there was some temporary relief of pain the arthritis was not materially affected.

There certainly are a few post-traumatic cases with cold pain, vasospasm and poor nutrition of the extremity which benefit greatly by sympathectomy, though whether it is wise to invoke the mechanism implied in the term reflex sympathetic dystrophy is another matter

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ABSTRACT

REFLEX SYMPATHETIC DYSTROPHY OF THE UPPER EXTREMITY

FREDERIC JAMES KOTTKE

Atraumatic periarthritis of the shoulder, or the shoulder-hand syndrome with painful limitation of motion of the shoulder and painful swelling and limitation of motion of the hand and fingers, is a fairly common condition This lesion usually develops slowly, progresses to the point where the shoulder and hand are severely incapacitated, and then persists for an indefinite period of time In the untreated cases the end result may be the complete loss of functions of the involved joints

Examination of the patient usually reveals that he has had some painful condition of a persistent nature which preceded the shoulder-hand disability Moreover, the majority of these patients have a low tolerance for emotional stress The basis of this disorder appears to be the establishment of a chronic reflex sympathetic hyperactivity in the upper extremity initiated by the pain This sympathetic hyperactivity results in impairment of circulation and nutrition of the extremity The joints become painful, edema occurs.

Interruption of the reflex pathway breaks this cycle and allows restoration of [illegible]

activity Interruption of the sympathetic pathways pharmacologically or surgically for a short period allows restoration of normal function of the shoulder and of the hand.

FIBROSITIS AND PSYCHOGENIC RHEUMATISM

FIBRO-FATTY TISSUE AND ITS RELATION TO CERTAIN "RHEUMATIC" SYNDROMES

W. S C COPEMAN

It is generally agreed that much of the pathology described for the chronic rheumatic diseases is speculative rather than factual Biopsy does not seem to confirm the current impression that muscle or fibrous tissues are generally the seat of cellular change in nonarticular rheumatism, or that inflammation is the underlying pathology

There is a third tissue of mesodermal origin, namely fat, which has seldom been considered in this connection but which appears to be quite commonly subject to pathologic variations that may cause symptoms which are labelled "rheumatic" Fatty tissue is widely distributed and constitutes nearly 20 per cent of the body weight It appears to be functional as well as protective, this being so, it would be strange if its functions were not sometimes disordered One of these functions appears to be concerned with water storage (The most striking example of this is perhaps seen in the camel's hump) It has been established in recent years by Bishop and others that human fat may retain water to a pathologic degree in certain disorders It would seem to be some derangement of this normal function of water storage which underlies the syndromes discussed in this paper

FIBROSITIS

Fibrositis as a clinical entity has for many years been accepted in the United States although its pathologic foundations are slender, resting almost entirely upon the theories of Gowers (1904), the equally unconfirmed histologic studies of Stockman (1920), and the suggestion of Elliott (1944) regarding muscle spasm as a cause Stockman defined fibrositis as "a condition of chronic inflammation of the white fibrous tissue of the fascial [illegible] characterized by pain and tenderness which may be local, widespread or referred, and is often associated with muscular spasm

Nature of the Pain in Fibrositis It was only comparatively recently that Lewis and Kellgren and others pointed out that the pain in fibrositis generally has its origin in certain focal points from which the more general subjective pain complained of by the patient is referred according to a segmental plan These trigger points, which when palpable are termed "fibrositic nodules," are not merely tender spots, which are also commonly found, but they are specific points at which real pain is produced, and [illegible]

frequently found,
view.
Sharply lectures
(1949), has emphasized the liberation of medical thought which has resulted from the substitution of syndromes for "disease entities" as units of illness. The syndrome has its philosophic basis in a chain of physiologic processes, interference with which at any point produces the same impairment of bodily function. He points out that the same syndrome may thus

clusions put forward in this paper are thought to explain more than a proportion of cases It will also be apparent that an etiologic classification will be unlikely of attainment in this field. It would seem that the only objective sign of the disorder lies in these localized trigger points which are, moreover, sometimes palpable in the form of nodules; it seems reasonable therefore to attempt to classify fibrositis according to the anatomic nature of the nodule, where this is known or strongly suspected.

Etiology of Trigger Points and Nodules It was observed (1941) that the pain in the back which accompanies most pyrexial illnesses is of the same nature and pattern as in fibrositis It has also been shown that although the pain disappears with the cessation of pyrexia, the tender trigger point will persist in a proportion of cases, often for very long periods and unknown to the patient. These trigger points can be reactivated by a recurrence of pyrexia, even if this be due to a different cause. It is suggested therefore that the tissues in which trigger points and nodules subsequently occur in the course of fibrositis may sometimes have been "sensitized" earlier in life in the course of an attack of influenza or one of the exanthemata The nature of the lesion may be a recurrent edema painfully distending certain fat lobules in the deep subcutaneous tissues It has also seemed certain that trauma, and probably also the direct action of cold, can be causative of similar lesions or can at least precipitate their development No evidence of the direct causative effect of focal infection has been established.

Fibrositis Due to Edematous Changes in the Fibro-fatty Tissues in Certain Sites The frequency of the occurrence of fibrositic pain of the lower back in otherwise healthy young soldiers first stimulated our interest in this matter. As a first step exact measurements were taken of the site of these trigger points or nodules in a large number of patients and a pain chart was plotted The back of every patient who died in hospital was systematically dissected and special reference was made to these areas The pain chart which evolved as the result of plotting the site of the trigger points or painful nodules in our series of cases of lumbar fibrositis was found to outline the erector spinae muscles, the crest of the iliac bones and the sacro-iliac joints It was later found that this chart also corresponded with areas in which residual fat occurred, even in cases with the grossest forms of cachexia.

As no evidence of pathologic change could be found in fibrous tissue or muscle in biopsy material, we decided to examine the deeper layers of fat which constituted the remaining tissue in the neighborhood of the trigger points In our first case we noticed a curious herniation of a large lobule

of distended fat through a defect in the deep fascia In a later biopsy of an easily felt and tender nodule, from which widespread pain was being referred, we discovered by cautious dissection that the nodule in this case was an edematous-looking node of fatty tissue lying among superficial fat of the upper buttock, but with a pedicle which could be traced down to the layer of fat lying beneath the deep fascia.

FATTY STRUCTURES AS SITES FOR PAINFUL LESIONS

In our original paper (1944) we described the areas of fat as being in the main "residual," in the sense that lobulated fat remains in these areas even when it disappears from other areas as the result of extreme cachexia The color of this residual fat in such cases we noted as being often darker or pinker than that of ordinary fat In two cases we were able after death to trace the pedicle of a superficial fat hernia down to the paranephric fat mass. These observations suggested that the areas of fat liable to be affected, at any rate in the lumbar region, might bear some relationship developmentally to the primitive renal fat gland around which from a comparatively early period of embryonic development fat congregates in closely lobulated clumps The well-marked area of residual fat which lines the rim of the ilium may not be covered by this hypothesis, although another primitive fat organ in the outer groin is described by some textbooks The largest of these fat organs is said to be situated between the scapulas, a position which seems to correspond with that of our dorsal fat pad.

Normal Anatomic Disposition of Fat Subcutaneous fat exists very generally throughout the body although its distribution is not uniform In certain situations it collects more abundantly and forms a considerable layer beneath the reticular layer of the corium where it is laid down in the subcutaneous areolar tissue as panniculus adiposus The areolar tissue forms a thin, indistensible, fibrous capsule around the large lobules. The lymphatics serving fat accompany the blood vessels in very close relationship as they enter the lobule There are numerous sensory nerves to the blood vessels, and possibly to other structures in the lobules, and sympathetic nerve fibers which run to the fat cells control the function of storage and yielding Where the skin is thicker and less movable, the reticular layer is fixed to the deep fascia by numerous stout fibrous bands (retinaculum cutis), the space between being filled with firm fat-cluster This formation normally occurs mostly on the posterior aspects of the trunk and the upper and outer aspects of the limbs

Pathologic Herniation of Fat Lobules From the brief account which has so far been given it will appear that what pass as fibrositic trigger points can often be shown to be related topographically in the lumbosacral region with the basic fat pattern Where these tender points were surgically explored, herniation of distended fat lobules through deficiencies in their investing fibrous covering was frequently found Removal or disruption of these hernias in such cases provided lasting relief from pain Histologic examination of the material removed has shown nothing but normal fat tissue distended with edematous fluid, this suggests that the cause of this edema is not inflammatory

In the lumbosacral region the fat hernias seen so far have been of three types (1944), pedunculated, nonpedunculated and foraminal The first two are self-explanatory, the herniation occurring from the deeper layer of

fat through a fascial covering or layer into a more superficial layer. The foraminal hernias occur along the foramina which exist in the deep fascia of the sacrospinalis muscles along which pass the lateral branches of the posterior primary divisions of the first, second and third lumbar nerves together with a small artery and vein.

Twenty-two selected case histories have been published (1944, 1947) from our series in which removal of a fat hernia of one of these types resulted in a permanent cure of the pain, and many subsequent unpublished cases have been investigated with similar findings and results Hertz (1947) working in Cleveland has confirmed this work and has published two further series of successful cases

Lesions Other Than Herniation Occurring in Fat of Normal Distribution

UPPER DORSAL REGION The skin is normally six to eight times thicker in this area than in most parts of the body, and islands of fat may be found actually in the reticular layer of the corium of patients suffering with panniculitis In the upper back the fibrous projections between the corium and the deep fascia normally form a series of honeycomb-like compartments which are filled with vascular fat. The axes of these "cells" are roughly parallel with the tension (cleavage) lines of Langer. This structure is particularly noticeable in the upper back area and we have called this diamond-shaped area the "dorsal fat pad." It is one of the common sites of "fibrositic" pain, and its area corresponds fairly accurately with that of the trapezius muscle which lies beneath it When painful nodules are palpable, as is commonly the case in "fibrositis" of this region, they are seldom fibrous in nature Biopsy will generally disclose the nodule to consist in the fatty contents of one or more of these compartments, swollen and under tension Negative evidence is afforded by the well attested observation that palpable nodules of this type can be "rubbed away" by means of deep massage, a fact that could not be rationalized if they were formed of solid material such as fibrous tissue.

PERIARTICULAR FAT PADS Localized collections of fat are to be found normally in association with certain joints, particularly the knees and ankles, and these may become painful without the joint itself necessarily being affected When this occurs an irresponsible diagnosis of arthritis is often made as the result of insufficient examination.

THE PATELLAR FAT PADS A normal intracapsular fat pad is situated between the joint and the patella This infrapatellar pad may become tender and painful without the joint itself being affected, particularly around the time of the menopause It is this lesion which commonly gives rise to the ... considered to imply

the joint cavity. No doubt in certain cases, if this is also affected, intra-articular function will to some extent be deranged

THE POPLITEAL FAT PAD This has not so far as I am aware been described as a separate entity *It is nonetheless present in more than 80 per cent of* normal people over forty years of age When it attracts notice by enlarging ... enlargement

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cause of pain and tenderness appears to be rather in the distention of the fat itself In these circumstances, however, full flexion of the knee joint by compressing the fat pad may give rise to pain and, again, to a mistaken diagnosis of arthritis.

THE SACRAL FAT PAD This structure can be observed in about 10 per cent of normal persons In structure it is very similar to the dorsal fat pad It is rather smaller than the sacrum but is of the same shape and lies over it It sometimes enlarges painfully as an isolated phenomenon, but more frequently in association with a general condition of panniculitis, either with or without obesity.

OTHER FAT PADS. Two other small fat pads exist in many normal persons and in all who are obese The first is situated over the dorsal surface of the basal phalanx of the great toe It seems to buffer the strong action between the tendon extensor hallucis longus and the skin It is seldom of clinical significance The other fat pads which seem to be of some significance, in so far as they often become swollen and painful in obese persons, are situated at the ankle joint Medially there is one between the malleolus and the heel, roughly over the flexor retinaculum while on the fibular side one lies over the stem of the inferior extensor retinaculum A further fat pad sometimes develops over the adductor tendons of the thigh at their pubic origin It is rather doubtful, however whether these can be considered to be of normal occurrence. They always develop in cases of obesity and may be very painful.

CLINICAL EFFECT OF ALTERING VOLUME AND DISTRIBUTION OF BODY FLUIDS

If the views which have been propounded are correct regarding the role of increased fluid tension in certain tissues causing pain, it should prove possible to relieve the pain by reversing this process An experiment was accordingly planned with Pugh (1945) whereby twenty-two cases of fibrositis, in which we believed that the pain might be of this type, were selected In these patients we induced the state of clinical dehydration, at which point we added electrolyte to the extracellular fluid to increase its osmotic pressure. Since the cell membranes are impermeable to sodium and chloride, intracellular dehydration would result

Methods The fluid intake of these patients was restricted for thirty-six hours to about 225 cc After this for a further twenty-four hours they were allowed neither food nor drink and their fluid output was increased by the administration of ¼ ounce of sodium sulfate at hourly intervals for six doses The process of dehydration could be followed by noting the daily loss of weight which varied between 1 and 3 5 kg This preliminary stage of dehydration was followed by an intravenous injection of 50 cc of 30 per cent sodium chloride into a vein Immediately after this injection the patient was allowed to drink 4 ounces of tea to mitigate thirst Apart from this no fluid was permitted for four hours after which no further limitation was imposed and the patient was encouraged to get up and about

Results Of the twenty-two patients thirteen were rendered completely free of pain for variable periods It was thought that this experiment confirmed other evidence as to the nature of the mechanism of the pain suffered in the successful cases

PANNICULITIS

Relationship of Panniculitis and Fibrositis. According to Stockman pain of unknown origin occurring in mesodermal tissue, which he believed was always due to inflammation of the white fibrous tissues, is covered by the generic term "fibrositis." Pain which has been described above as occurring from the distention in normally situated subcutaneous fat lobules can also therefore conveniently be classified under this heading. Where the pain of this type occurs in abnormally deposited fat, however, it will be referred to as "panniculitis." The condition was described by Stockman (*1911*) *and also by Telling.*

Panniculitis is a common condition, it is insufficiently recognized as a cause for pain which is not infrequently labelled "psychogenic." Our investigations have shown no single instance, histologically, of an inflammatory reaction having occurred, and we believe that the pain in this condition originates as the result of edema, and consequently distention, of *lobules of the abnormal fat deposits Panniculitis can best be considered* in relationship to those regions of the body in which it is most commonly encountered, namely, the upper dorsal region, the upper and outer aspects of the limbs, around certain joints—especially the knees, elbows and ankles —and some other sites. Panniculitis is often associated with general obesity Even in cases showing this association the sites of pain generally remain confined to the regions in which pain is situated in cases not so complicated This localization of the pain in cases of general obesity may be due to the less lobulated nature of the fat which is laid down elsewhere and also to the fact that in other sites, such as the abdominal wall, no fibrous fascia or capsule is present to limit the distention of the fat if it *becomes* [illegible] with obesity.

[illegible] he preceding

[illegible] areas of pain

The nodular feel of the fat deposits, the fluctuation in the sites of pain, and the histologic findings, however, suggest that the underlying cause of the pain may be the same as in the preceding syndromes, namely, a shifting noninflammatory edema affecting the pathologic fat deposits

Panniculitis of the Upper Dorsal Region The dorsal fat pad which has been described as the seat of local lesions in fibrositis is more generally involved in cases of panniculitis The tissues are sometimes *successively* thickened and the subcutaneous tissues cannot be lifted between the finger and thumb.

Panniculitis of the Upper and Outer Aspects of the Limbs. Tender nodules not infrequently form along the upper and outer aspects of the thighs, often in association with enlargement of the periarticular fat pads of the knee Pain due to this cause is generally diagnosed as fibrositis The usual situation of these localized collections of fat is in the panniculus adiposus where certain portions of the areolar tissue seem to become more heavily charged with fat than do others These portions appear to be more closely lobulated and independent of the average layer of fat at *this level,* and give the appearance of being small independent "mesenteries," each with its own blood and lymphatic supply There is also a large potential space *between the superficial and deep layers* of the fascia which overlies the fascia lata of the thighs, and fat nodules sometimes form also in this space

In cases where these collections become painful, it is found that they have become circumscribed by adhesions which appear to prevent lateral extension of the fat mass. The cause of these limiting adhesions is unknown—it may be traumatic—but since their occurrence appears to be related in many cases to the menopause they may result from a drying up of the normal lubricating fluid of the fascia.

Knee Joint. An abnormal fat pad develops over the inner aspect of the knee joints as a menopausal manifestation, and perhaps as a precursor of ultimate

although frequently pain or tenderness is confined to one side. On palpation distinct lobulation of the contained fat is easily felt, and it can be appreciated that only certain lobules, which feel more tense, are tender This localized tense tenderness affects different lobules on different days, and therefore appears to depend upon a condition of shifting edema which moves from lobule to lobule Excision of the painful fat pad successfully relieves the pain. Microscopic examination shows only edematous fat of normal structure and with no cellular reaction These pads are not to be considered as lipomata. The arrangement of this areolar tissue does not

fact, discrete clumps each with its own blood supply and lymphatic system.

When these medial fat pads attain a large size they can interfere considerably with the free function of the joint, and pain from them is quite frequently referred to the joint itself subjectively, although careful objective search will reveal a tense periarticular fat lobule in the pad as its real origin The differential diagnosis of arthritis is too often made in such cases, particularly if the normally occurring age changes are interpreted as radiologic confirmation of this view

ETIOLOGY OF NONINFLAMMATORY EDEMA

The cause for the noninflammatory edema which is found locally to be distending the fat lobules (which in turn cause pain in the type of fibrositis which has been described and in panniculitis) is unknown. It

ction of fat-water metabolism,

with obesity. It is this factor

use inexplicable variations in

weight which occur during the dietetic treatment of the obese. In view of the frequent association of these syndromes with the female menopause (both natural and artificial) it is tempting to suspect that the underlying cause is endocrine. It seems to be accepted by endocrinologists that excessive secretion of estrogens in the human body will result in water retention which largely affects the fatty tissues. The fault here may lie in the dysfunction of the ovaries, or more probably in the pituitary body or the hypothalamus The latter probability is strengthened by the fact that men also suffer with these syndromes, more particularly the fibrositic one Overactivity of the pituitary or the adrenals is known to be associated with pregnancy and the climacteric and commonly results in obesity In most cases, however, no

localized panniculitis the affected area may be thoroughly infiltrated with an oily anesthetic solution such as benzyl benzoate under pressure, with the same object in view. The fibrous compartments separating the fat lobules should afterwards be disrupted with the cutting edge of the wide-bored needle employed, to prevent recurrence.

Surgery. Surgery has no place in fibrositis in which herniation is not a cause. Removal of irreducible fat hernias which cannot be disrupted by injection, however, remains the logical procedure, and in well chosen cases is highly successful. These structures are sometimes surprisingly difficult to locate in a well covered person, however, and local anesthesia is essential since the patient's subjective impressions are often necessary to ensure that it has been rightly localized It must not be forgotten that herniations are sometimes multiple. In cases of panniculitis with obesity, persistent pain which cannot be remedied by other means can sometimes be cured surgically by undercutting the painful area Presumably the sensory nerves responsible are cut in the course of this procedure.

Several papers have been published in America during the last few years confirming the role played by fat hernias in the causation of pain in the lumbar and gluteal regions. The largest series is that of Hertz; in a personal communication (1948) he stated that since 1944 his series of such cases had reached a total of 229, of which he had operated upon sixty-eight. At this last follow-up sixty-two of these had maintained complete relief from pain Hutcherson (1948) reported forty-two such cases operated upon, with permanent relief of pain in forty. In England I have received accounts of isolated operations of this type which have been followed by success. Among surgeons who have communicated with me in this way I wish to thank Messrs Leo Norbury, S. L. Higgs, Rodney Maingot, Harold Edwards, J C. R Hindenach and David Trevor.

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SOME ASPECTS OF PSYCHOGENIC RHEUMATISM

WILLIAM TEGNER

We who work with patients suffering from "rheumatism" have long been faced with the problem of the patient whose aches and pains do not fit in with any recognized anatomic syndrome Before the war we became more and more conscious of the fact that many of our patients were presenting a symptomatology that fitted no known organic disease and whose physical signs appeared to be trivial or were absent. Many such patients were to be found in the very large numbers of rheumatic patients attending the London Hospital and for want of a better term I coined the phrase "polyalgia syndrome" to describe them. Previously the tendency had been to [illegible] to be not only a sign [illegible] was a slur on the true [illegible] of fibrositis. [illegible] tribution on the relationship between the psychologic and physical characteristics of patients suffering from arthritis. In England, in 1942, Ellman, Savage, Wittkower

and Rodger[2] analyzed fifty patients who had been diagnosed as suffering from fibrositis and found that twenty-three of these had no physical signs of disease and twenty-five of them manifested hysterical tendencies, these workers were interested in seeing how far psychologic factors could produce organic changes. In 1945 Flind and Barber[3] published an important paper with the significant title "The Psychogenic Character of Some So-called Rheumatic Pains" In their paper one finds a good description of

England revealed that rheumatic, it was unfortunate for rheumatism that, owing to there being no rheumatism centers in the British Medical Services, the work on this subject was carried out by psychiatrists and was not willingly accepted by the more somatically-minded rheumatologists.

In the first 500 cases of rheumatism seen by me on return to civilian practice after the war I found that in sixty-six (13 per cent) the only possible diagnosis was psychogenic rheumatism This was the third most common group in the series The sex incidence of my series was two women to one man In the war series, men, of course, were heavily predominant There is no doubt that psychogenic rheumatism can affect men exactly as it does women It is the general experience of civilian rheumatism clinics that women patients outnumber men In postwar England there is every reason for women to develop functional illness more readily than men for the burdens of life are far greater for women, the struggle for existence causes them very great difficulties

If psychogenic rheumatism is so commonly met by those who handle large numbers of rheumatic patients, the existence of this condition must be adequately acknowledged and its manifestations recognized I think there are two great needs in the sphere of psychogenic rheumatism first, agreed criteria of diagnosis, and second, a satisfactory method of treating and disposing of these patients

DIAGNOSIS

The diagnosis of psychogenic rheumatism depends largely on the history given by the patient and the attitude adopted by him when the history is taken The vague nature of the history, the fanciful description of the sensations which are experienced and the quaint symbolism used in the description of the symptoms are all characteristic of the condition In psychogenic rheumatism the diffuse, shifting pain which is experienced is something peculiar and personal to the patient, it is valuable and not common to other more ordinary sufferers This point must be raised again when we discuss treatment, but it is of great importance and must be kept in mind One can add little to Hench and Boland's admirable diagnostic criteria[4] expressed in their table for differentiating between the symptoms of fibrositis and those of psychogenic rheumatism While some workers suggest that the absence of physical signs is characteristic of the condition I think this is not absolutely true, for these patients do in fact present many typical physical reactions which are of great value in establishing diagnosis They are usually exhibitionists and physically very tense and find it almost impossible to relax While their deep reflexes are exaggerated they show no other neurologic signs of upper motor neuron lesions

Again, on examination they may react in one of two diametrically opposite ways: they may either resist and resent examination, or they may exhibit the self-prodding phenomenon and even seize the doctor's fingers and plunge them into the so-called tender areas. These tender areas, which have misled physicians into regarding them as areas of fibrositis because of tenderness on pressure, are often in fact areas of cutaneous hyperesthesia. Just as some hysterical patients react with cutaneous anesthesia which is readily demonstrated, the cutaneous hyperesthesia which others show can be demonstrated either by stroking the skin or by pinching the skin away from underlying tissue, which will elicit a pain similar to that brought out by deep palpation. The painful areas of which the patient complains will probably have no true anatomic background for the psyche knows no anatomy. Laboratory and radiologic examination will help in excluding organic disease.

It may be, of course, that one meets the second type of sufferer, the one who, while having a fundamental organic lesion, exaggerates the symptoms by psychogenic overlay. In such cases it is important to assess the relative pre[illegible] findings suc[illegible] of psychog[illegible]

TREATMENT

The handling and disposal of these patients is of the greatest importance and presents a problem which so far has not been adequately studied. The patient's symptoms are of great value to him. If he attends a specialist at a hospital he ceases to be as other men are and becomes, in his own opinion, some one of interest and importance and a sick man who must be looked after. Response to treatment of any kind other than psychiatry is therefore very poor. While one set of symptoms may be relieved, it will be replaced by another. These psychogenic rheumatics have a remarkable success in getting things their own way, a point so well brought out by Flind and Barber.

The attitude of the psychiatrist is not always helpful; some of them will not agree that the general physician is competent to diagnose a psychogenic illness without the opinion of a trained psychiatrist, but at the same time, after agreeing with the diagnosis, will explain that the situation has gone beyond the reach of psychiatry and that nothing very much can be done. In England, under the National Health Service, treatment for illness is the right of every citizen, the patient is therefore referred for physiotherapy. But one must agree with Hench and Boland that physical therapy tends to convince patients that they are suffering from organic disease, and would therefore in this case seem to be contraindicated.

In my Department at the London Hospital we have a heavy load of patients with psychogenic rheumatism and my present line of attack on the problem of their disposal is to organize group therapy as far as possible. In the early days I ordered the groups general exposure to ultraviolet radiation from the carbon arc lamp followed by group exercise. This was only partially successful and the next stage is being worked out with the help of the psychiatrists, from whom I am receiving great encouragement. The aim of group therapy is to organize discussion groups among the patients. They see the exaggerations and discrepancies in the complaints of the others

and are encouraged to discuss them This may lead to some heat in t discussions and the psychiatrist is there to see fair play and to preve heated discussion becoming too heated This form of treatment is still the experimental stage but it has the advantage of being more econom than individual psychiatry.

I suggest that, in future, rheumatism clinics will have to make arrangements whereby facilities are available for the group treatment of sufferers from psychogenic rheumatism These will have to be run in conjunction with psychiatrists and will have to be situated either in the rheumatism clinic or, by arrangement, at psychiatric centers

THE NATURE OF PAIN IN PSYCHOGENIC RHEUMATISM

What is the nature of the sensation of which these sufferers complain? Their own descriptions are not very helpful The so-called pain may, on the one hand, "burn like fire," but it is very often "a numb pain" which would seem a contradiction in terms Can it be compared with organic pain or is it completely different? The organic die-hards believe very firmly that there is a physical basis for the pain however much it may be exaggerated I was warned before leaving England not to interest myself too greatly in psychogenic rheumatism as "it always turns out to be organic in the end"! The response to treatment gives us some clue to the nature of pain These patients do not respond to analgesics by mouth, local injection of anesthetic, while it may produce temporary alleviation of localized symptoms is almost invariably accompanied by extraordinary general manifestations such as faints, palpitation and disorientation These general symptoms are usually proudly held out by the patient as being evidence of the seriousness of his illness Much work is being done on pain and there is some evidence that we can distinguish the commoner surface pain from deep referred pain The physiologists who investigate deep pain tell us of its severe and intolerable character While psychogenic sufferers often tell of the intolerable character of their pain I am always struck by the fact that they do not appear to be patients who are suffering severely They show none of the signs of exhaustion which one expects as the result of prolonged severe pain I think it is difficult to express psychogenic pain in our organic terminology and I can only suggest that there is something ecstatic in the nature of the sensation of which these patients complain

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THE ROLE OF PSYCHOLOGIC FACTORS IN FIBROSITIS*

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This fibrositis syndrome may be seen as "secondary fibrositis" where there is an obvious cause, e g, trauma, or as "primary fibrositis" when the cause is not apparent The content of this idiopathic group, primary fibrositis, will vary with the accuracy of diagnosis. Physical diseases such as herniated intervertebral disk or trichinosis, if unrecognized, may be thought to be cases of primary fibrositis. Similarly, psychoneurotic disorders may be mistaken for cases of primary fibrositis This latter danger has been emphasized lately and such cases of psychoneuroses have been assembled under the term *psychogenic rheumatism*[2, 3] *This term has arisen within* the circle of medical specialists in rheumatism and may be defined as those cases of psychoneurosis which are obvious to a rheumatologist.

These diagnostic difficulties cast their shadows over any discussion of primary fibrositis, each clinician's understanding of the state will be impaired by the error of his unwitting mistakes in diagnosis Conversely, any useful consideration of fibrositis must be based on cases in which no pathogenic factor has been overlooked Now the fibrositis syndrome is a symptom complex of bodily distress and stiff action, and people can become physically sore and stiff from mental as well as physical trouble. Accordingly, a reliable study of primary fibrositis would seem to require a broad survey of psychologic and social factors as well as the physical *factors in* all cases

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With these considerations in mind the authors are making a study of primary fibrositis as defined above, i e, fibrositis with no obvious physical causes and with psychogenic rheumatism excluded. These patients are selected by one of us (W.G.) as they present themselves in the practice of a physician specializing in rheumatic diseases Another of us (H C S) then conducts a broad clinical examination that includes general medical, neurologic, psychiatric and rheumatologic surveys The third author (J A.W.) has acted as consultant for special psychiatric and neurologic *problems* With such a team we are attempting to study these patients in a way that may be reproduced by a general physician with consultation when necessary. What is needed is time and a training which permits a clinician to pursue his inquiry and examination into physical and psychologic and

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multiple and may involve both peripheral physical faults and central psychologic faults.

On the physical side we know that *prolonged tonic action of a muscle* will produce aching and tenderness and trigger points Our eleven patients who developed the fibrositis syndrome while in mental attitudes of emotional restraint felt unrelaxed in themselves and they described their bodies as if constantly limited by some extra muscular activity. They felt tense and tightened up Their shoulders seemed to be held higher. Their limbs felt controlled and held back They, in themselves, did not feel at liberty and their physical motor system seemed to be equally under some mild restraint We have not yet attempted to study the intimate state of local muscular action and tone by physiologic instruments, but clinically we gain an impression of an increased tautness in those muscles which cooperate in emotional attitudes. We also know that in these patients this motor state comes and goes with the rise and fall of emotional tension We know that *with suggestion and massage these patients may relax psychologically and* that the muscles then feel slacker and more comfortable As the starting point for considering the local neuromuscular fault it seems likely that when a person is tense with *emotional restraint* his muscles may remain in some extra tonic action as physical components of his total behavior and adaptation to the situation he faces In some unknown way this hypertonicity must lead to, or be accompanied by, the activation of those pain mechanisms which produce the fibrositic syndrome. The stiffness is a direct expression of their inability to act in an unlimited fashion

Here we cannot be put off by any assumption that these fibrositic aches and pains are other than peripherally produced When the clinician has carefully excluded pain and suffering of a central and hysterical order, there will still remain clinical evidence to suggest that the patient is *suffering from pain of peripheral origin Frequently the clinician* will be able to observe that the tenderness is confined to single muscles rather than to regions of tissues, e g , a muscle such as the extensor carpi radialis longus may be clearly defined by palpating for tenderness when no other tissue in the forearm is tender This points to a local disorder in that muscle or its peripheral innervation, since hysterical pain and central pain are never confined to a peripheral anatomic unit It is very unlikely that individual muscles have a sensory or motor representation within the human cerebrum And while we can mentally perceive regions and areas of our body we cannot discriminate an individual muscle in tonic action

Neither can we be put off by any suggestion *that psychogenic rheumatism* is completely separate from the fibrositis syndrome In the stream of a neuropsychiatric practice one often sees the full-blown state of fibrositis in psychoneurotic patients while they are suffering unexpressed emotional tension The state of their muscles and fibrous tissue may exactly duplicate the fibrositis syndrome with aching muscles, soreness and stiffness, tender muscles and trigger points They may develop exquisite radiating pain from pressure on trigger points or nodules or spontaneously *And as these* patients find peace of mind and relaxation this fibrositis syndrome disappears

If, then, we can assume that emotional restraint may maintain motor attitudes which lead to peripheral pain, what do we find in cases of secondary fibrositis from physical causes? In the case of trauma it is likely

that the injured part is splinted by tonic muscle action. With infection we have observed the localization of tenderness within individual muscles and have found the trigger mechanisms established in the muscles that were sore. When a nerve root is irritated as by a herniated intervertebral disk, the peripheral muscles and other tissue supplied by that nerve root may demonstrate the complete fibrositis syndrome limited to this radicular distribution.[4] The physiologic changes here are obscure but it is not improbable that an early effect of root irritation is an increased tonic action of the muscles in that segment.[5]

These clinical observations may be the slender threads that lead to an understanding of how the fibrositis syndrome becomes established under mental as well as physical strain. The starting point would be a state of muscular hypertonia which, when maintained, somehow stimulates muscle pain mechanisms to produce the aching and tenderness, and stimulates nerve reflex mechanisms to produce the trigger points and referred sensations.[6]

These speculations do not set forth an explanation of fibrositis but rather represent a tentative working hypothesis which may lead to critical clinical and experimental studies. This whole subject of fibrositis is marked by very few established facts, a great lack of basic knowledge, and an extensive literature that proclaims our confusion. Broad clinical studies of primary fibrositis are essential before we can know exactly what the problem contains. The psychoneuroses with fibrositis syndrome have still to be adequately described. Physiologic studies of the neuromuscular state in fibrositis are too scanty to permit more than speculation. The pathologic anatomy of fibrositis is not established, and if we place muscle hypertonia as the essential feature leading to the pain and stiffness then we must explain why other hypertonic states do not always lead to a similar painful state.

Turning now to the central psychologic fault, several remarks may be made about the case material we have studied. It seems unlikely that we are dealing with one personality type or one pathogenic emotion. The essential factor in the mind-body relationship seems to be the mental and physical state of restraint which was hated and resented but was accepted and maintained. They did not want to hold themselves in but they could not let themselves out. This is emotional behavior not unlike the involuntary attitudes of a trapped, hostile animal. Such a state could be reached from a variety of psychologic developments. The personalities of our patients ranged from passive persons who were forced to be active, to very dominating people who were forced to be submissive. Their psychosexual development was varied. It included infantile and homosexual types of immaturity as well as others fairly mature. Compulsive habits and perfectionistic standards were encountered, but not always. These traits indicate a need for self-restraint and self-control, and it may be that such highly organized people are prone to develop the fibrositis syndrome. Meanwhile we must also keep in mind that all aggressive or submissive or immature or perfectionistic people do not develop fibrositis.

Similarly the emotional state our patients showed had some variations and much remains to be understood. The usual pent-up emotion was resentment, hostility or anger which could not be expressed. But intermingled were encountered tension from anxiety, fear, the effort of containing oneself, and the tension of frustration. Here too we must remember that plenty of people with pent-up anger do not develop any physical symptoms while in

others it may find expression in viscera such as heart or stomach rather than in muscles and nerves.

These variations of the psychologic picture again bring us face to face with unknown factors, with our vast ignorance in these matters. It is probable that people hold themselves in against their wishes for many different reasons and that generalizations cannot be made. However, in any one particular case study the story and sequence of the psychologic development and physical disability become clear as the facts are obtained. From our experience the main outlines of the situation can be grasped in an extra hour or so of history taking by a physician who has an understanding of human nature We believe that most cases will not require a special psychiatric opinion if the physician will take the extra time to gather the psychologic and social story

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PSYCHIATRIC STUDIES OF PATIENTS WITH RHEUMATOID ARTHRITIS

ALFRED O. LUDWIG

The following material was collected from three psychoanalytically studied cases seen for several hundred hours each, from nine less well-investigated patients, and from many single interviews with a number of other patients, all suffering from rheumatoid arthritis.

THE PERSONALITY PATTERN OF RHEUMATOID ARTHRITIS

A personality pattern was found which was constant for all the cases of rheumatoid arthritis studied The personality pattern observed is not specific for patients with rheumatoid arthritis, but has also been noted in patients with other psychosomatic disorders (simple obesity, Raynaud's disease, and ulcerative colitis),[1, 2] and is closely similar to that described by Kardiner in individuals with chronic traumatic neurosis incurred in war[3]

The outstanding feature is marked impairment of ego function, manifested by extreme dependence, insecurity, feelings of inadequacy, difficulty in the usual methods of mastering or coping with the environment and with other people, and severe blocking of the external expression of emotion, with internalization of feeling and autonomic overactivity.

These persons are usually unaware of their feelings of helplessness Frequently, they deny their dependence by overcompensating with an outward facade of independence, self-assurance, self-control, and apparent

shallowness of emotion. This gives the casual observer the mistaken impression that they are cold and devoid of feeling and that there are no emotional conflicts. Along with the inner insecurity, the world seems to them to be a hostile place which constantly threatens to injure them. A strange person, a new situation, even slight changes within a familiar environment or in the attitude of a familiar person, seem to produce severe degrees of anxiety. This they usually describe as shyness, and self-consciousness, and a strong desire to flee from the unpleasant situation.

Their emotional lives are marked by an inability to establish close, meaningful relationships with other persons of either sex. Their own and others' feelings seem to be regarded as potentially dangerous, and in consequence, all emotional closeness with other people is avoided. They are keenly intuitive and acutely aware of the feelings of others and they sense and react immediately to the slightest criticism or rejection which they feel directed toward them.

Their insecurity and need for support and love from others makes them extremely cautious of their reactions toward other people, and they appear to be in constant fear that any false move on their part may result in rejec-
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appears in its place.

In patients with rheumatoid arthritis, the most characteristic evidence of this type of overactivity is the presence of vasomotor symptoms. They were present in 200 of a series of 293 carefully studied cases of rheumatoid arthritis at the Massachusetts General Hospital. Gastro-intestinal disturbances and palpitation without other causes are not infrequent and probably represent another manifestation of autonomic overstimulation.[4]

DEFENSE MECHANISMS

These patients habitually employ a number of psychologic and psychosomatic defense mechanisms in their effort to deal with the constant severe inner
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the onset of the illness many of them have been exceedingly hard driving and overly conscientious. It is very difficult for them to sit still, and they

attempt to negate their dependence both by accepting far more responsibility than they can handle, and by overwork. This response probably originates as well from the fear of losing the regard and support of others. They drive themselves harder and harder in their struggle against the fear of failure and the loss of support. Other patients manifest their dependence and inadequacy openly, avoid all responsibility, and rely completely on

others for guidance Such patients are prone to be excessively and openly demanding of everyone around them, and often succeed in tyrannizing their families and medical attendants by means of their illness. This pathologic overactivity is accompanied by a high degree of emotional fatigue incommensurate with the amount of physical energy expended.

Another mechanism used to alleviate anxiety and relieve tension is the abnormal ingestion of food, and not infrequently of drugs or alcohol One of my patients overate compulsively in response to even minor frustrations, another became addicted to alcohol Obesity was present in 5 6 per cent of our Massachusetts General Hospital series [4]

PRECIPITATING FACTORS

The single most important precipitating factor in the case material was the loss of or separation from important key figures on whom these patients depended for support This might be by death but often only by separation from or following rejection by such a key person Such an injury is invariably followed by a grief reaction, but without any, or with inadequate, outward expression of sadness or of weeping The term "bereavement" is used in this sense with a broad meaning and implies the reaction to any loss Such loss may be not only by death of a person close to the patient, but may also be represented by loss of financial security, loss of position, loss of status in the community, by leaving home by exclusion from a group, and even by bodily injury or minor operations In some women patients, menstruation and childbirth appear also to have the psychologic significance of loss in this sense

Not only were such losses important in correlation with and immediately preceding the onset of the disease, but exacerbations frequently occurred on the anniversaries of the deaths of relatives, or indeed by other events associated psychologically with the original bereavement

The bereavement reaction is usually accompanied by moderately severe depression These were frequent in my cases Suicidal ideas are not uncommon but these patients appear to be protected against suicide and depression both by the appearance of renewed symptoms of the disease and in some instances by the ingestion of food or drugs as described above

RELATION TO PSYCHOSOMATIC GASTROINTESTINAL DISORDERS

In all the cases observed, there appeared to be a significant correlation between rheumatoid arthritis and psychosomatic disorders of the gastrointestinal tract These include abdominal distress, excess peristalsis, nausea, vomiting and diarrhea, occurring at times of emotional stress In one of my patients, a peptic ulcer, overeating, and obesity began at the same time as the onset of arthritis In the Massachusetts General Hospital series of cases, peptic ulcer occurred in 3 6 per cent of 293 patients [4]

FAMILY BACKGROUND

In general, the parents of these patients appear to have been unstable and unable to provide an adequately secure emotional environment for the patients in childhood The mothers of the patients could not furnish an atmosphere of warmth and affection for them in infancy and childhood They were frequently excessively rigid in their early training of the patients, and in some instances, openly rejecting and hostile. In other cases, the mother's relationships with the patients were marked by overanxiety and

overprotectiveness, and resulted in unduly prolonged and marked dependence upon her.

It is important to note that both the emotional insecurity and dependence, as well as the disturbance in relationships with others and the emotional isolation, were present for many years before the onset, and not merely secondary to the disease itself

TREATMENT

Psychotherapy with these patients involves considerable technical difficulty It is not easy to establish emotional contact with persons who are so extremely insecure and so frightened of any contact with others. A very warm, friendly, and informal approach is indicated It is extremely difficult to lead them into a discussion of meaningful emotional material Once a strong positive relation was established, it was possible to observe and correlate their reaction to rejection, disappointment, and frustration with their bodily symptoms and to show them that they expressed their responses almost entirely by unconscious autonomic activity, rather than by conscious, adequate, external emotional release During the course of therapy, numerous instances of such internalization could be observed and demonstrated to the patient, who slowly became able to translate the primitive somatic expressions of feeling into outward release Many instances could be observed in which strong internalized emotion appeared to be followed by exacerbations in joint pain and on a few occasions in the appearance of joint swelling, as well as of other psychosomatic symptoms such as vasomotor and gastro-intestinal disturbances Grief, sadness, and weeping for important figures lost sometimes many years ago finally reached full expression with considerable relief of tension

CONCLUSIONS

There is evidence that persons who succumb to rheumatoid arthritis suffer from extreme degrees of emotional immaturity and feelings of insecurity They react very poorly to frustration, rejection, and loss of support. They are unable to express their very strong emotions, but instead react to emotional crises with intense autonomic activity, in a manner which closely resembles the primitive and poorly organized technics of mastery by destruction and ingestion described in the traumatic neuroses

These preliminary observations indicate that emotional factors may play a very significant role in precipitating the onset and exacerbations in rheumatoid arthritis No conclusion can be drawn at this time as to the psychophysiologic means whereby joint function can be influenced by emotional conflict

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PSYCHOGENIC RHEUMATISM

EDWARD WEISS

A common problem in the practice of internal medicine is the patient who

fever and chronic brucellosis are frequent diagnoses. Attention is often focused on the slight rise in temperature and the patient undergoes repeated and prolonged studies from the standpoint of obscure infection or endocrine dysfunction. In the course of the many physical and laboratory studies slight deviations from normal are detected and additional diagnoses are made which add to the patient's concern She sees herself crippled by arthritis or heart disease and anticipates being a burden to her family In addition to the many physical and physiotherapeutic measures that are used in treatment, rest and more rest is urged upon the patient, which perpetuates the invalidism and leads to greater restriction and a more impoverished life This kind of story continues, sometimes for years, often with prolonged periods of hospital observation and sanatorium stay.

CLINICAL MATERIAL

These observations are based on a study of eighty-three patients encountered in a study of patients with chronic fatigue, because so-called psychogenic rheumatism is only an aspect of the chronic fatigue problem Of the eighty-three patients only nine were men. All but eleven of the women were married. Physical findings of significance were uniformly absent. Twenty-five patients had slight fever, always less than 100° F, and in only two was there slight elevation of the sedimentation rate. Neither leukocytosis nor any other important abnormality of the blood count was found Lowered metabolic readings were occasionally encountered and low normal fasting blood sugar levels, as well as somewhat flattened sugar tolerance curves, were rarely observed but it was always felt that these were secondary rather than causal features. The same findings were present after improvement.

Evidence for chronic brucellosis seemed positive in only one patient Low back pain of a nagging character was a frequent association, and atypical neuralgias of the face, shoulder region, and leg were frequently associated with the body aches and pains "Sinus infection" was almost invariably held responsible for headache, "focal infection" for the atypical neuralgia, and slight pelvic abnormalities for pain in the back

The referring diagnoses, in addition to arthritis, fibrositis, and muscular and nonarticular rheumatism, included tuberculosis, rheumatic fever, brucellosis and endocrine dysfunction (especially asthenia of thyroid and adrenal origin, adrenal cortical insufficiency being a frequent diagnosis). Hypoglycemia, low blood pressure, anemia and avitaminosis occurred again and again in almost every history Neurocirculatory asthenia and constitutional inadequacy were frequent diagnoses. Colitis, autointoxication, and autonomic imbalance were often mentioned If the patient was near middle age, climacteric was almost invariably held responsible, both in

women and men, so that injections of estrogenic substances or testosterone were almost as frequent as injections of vitamin B_1.

Psychosomatic study, meaning the simultaneous application of physiologic and psychologic technics, proved the presence of psychopathology rather than tissue pathology. Hysteria was encountered in thirty-seven patients, anxiety states in twenty-two, hypochondriasis in four, and two suffered from psychotic depressions. The latter two were helped by electric shock Eighteen patients could be classified as having neurotic character disorders The one patient with rather definite evidence of chronic brucellosis, as indicated by suggestive history and high titers in the agglutination reaction in addition to positive skin tests, had a pronounced personality disturbance which antedated the onset of the illness

Psychologic symptoms most frequently encountered were poor sleep and poor sexual adjustment, and a marital problem was the most frequent underlying problem Significant emotional conflicts were found which were apparently responsible for the fatigue, but a special feature associated with muscular aches and pains was the presence of chronic resentment of which the patient was usually totally unaware

DIAGNOSIS

Psychosomatic diagnosis means more than diagnosis by exclusion of organic disease. While it does not imply less study of the soma it does call for more study of the psyche It means the utilization of physiologic and psychologic technics simultaneously in an effort to establish a definitive diagnosis and in preparation for comprehensive medical care We do not have to change our history form, we only have to change our point of view to include this supplementary technic Diagnosis by exclusion is dangerous in these cases—it leads to greater invalidism To the organically minded physician there is always another possibility to investigate and thus he becomes a pathogenic agent in perpetuating the illness by his well meaning but mistaken and never-ending efforts to find a "physical cause" The problem is not so complicated that we cannot complete our physical studies [illegible]

[illegible] but in [illegible] be paid to the behavior of the patient and to the actual words that he uses in describing his complaints as well as the asides and apparent irrelevancies that so often give important clues to the emotional factor Other fundamental considerations are giving the patient time, allowing him to talk with as few interruptions as possible, avoiding extensive note-taking so that the patient may feel that you are more interested in him as a person than in the setting down of the history, showing interest and sympathy for what the patient sometimes regards as trivial or silly In addition, more attention must be given to the chronologic development of the life history with emphasis on the various factors in the childhood period that may [illegible]

[illegible] effort will be made to obtain a more complete picture of the family background[1]

In addition to aches and pains and stiffness these patients are always fatigued. Nowadays lack of energy is apt to be explained by lack of vitamins, but while these patients are sometimes too tired to eat and may not get an adequate diet, this is certainly not their primary problem. Indeed, *they may eat too much in an effort to overcome "nervous hunger."* What we must interest ourselves in is not so much a lack of vitamins as the lack of emotional satisfaction in their lives There must be some kind of a balance to the emotional life with too much expenditure on conflict and too little satisfaction coming in, the patient is headed for emotional bankruptcy

Instead of looking for focal infection we must look for focal conflict, and often we will find it in regard to a marital or parent-child problem Emotional conflict, which uses up energy that is then no longer available for work or social purposes, is the commonest cause of chronic fatigue. A special feature of the patients with muscular aches and pains is the presence of smoldering resentment. When it is brought to the surface, and their feelings somewhat relieved, improvement takes place. As Sherrington[2] expressed it, the best way to deal with tension of emotional origin is by *action, the next best way is by speech and the least effective is by thought* The person who says, "Oh, what is the use of fighting; after all she is my mother [sister, daughter]"—that person, who does not realize the amount of aggravation in her day-to-day existence and certainly does not know how angry it makes her or what hostile feelings she is accumulating, is unable to relax and her rebellion takes the form of constant muscle tension As Ellman et al [3] point out, the muscles serve as a means of defense and attack in the struggle for existence and thus internal tension is most easily relieved by muscular action When the external expression of aggression in the form of muscular action is inhibited by repressing forces, then muscular tension may result which is felt by the individual as pain and limitation of movement and is often erroneously interpreted by the examining physician as fibrositis or muscular rheumatism.

Halliday[4-7] has been chiefly responsible for calling our attention to *the syndrome of psychogenic rheumatism in civil medicine* In connection with his studies, Halliday found fibrositic nodules just as common in people who had no complaints as in those with so-called fibrositis, which is the diagnosis commonly applied to this syndrome in Great Britain

Elsewhere[1] the significance of organ language has been pointed out *When the person is unable to express his tension by word or deed, his body* sometimes takes over the function of saying things for him that he cannot say with his mouth Thus the person who is unable to swallow, but who has no organic disease, sometimes cannot swallow something in his life situation, and in the same way the patient with muscular aches and pains would often like to express his aggression against someone in particular but is prevented from doing so by the affection or respect for that person that is mingled with his hostility He translates the aches and pains of his life situation into bodily aches and pains Hence, persuading such a patient to talk about focal conflict may provide an answer to the problem

When patients are tense, taut, and uncommunicative, they *will often* begin to talk when they are put at ease and muscular relaxation occurs, of course the reverse is equally true, that when patients can be encouraged to talk their muscle tension often diminishes

PSYCHOGENIC RHEUMATISM

Pain in the lower back region is a diagnostic problem that presents many difficulties, and while today attention is focused on herniated disk, we must not forget that the syndrome of low back pain and fatigue is often an expression of emotional conflict which frequently occurs in association with pelvic preoccupation on the part of both patient and doctor Tired women with nagging or even "excruciating" pain in the back, who are overconcerned about some slight pelvic abnormality and who are eager to have it corrected by surgery, should be suspect from a psychosomatic standpoint and caution should be exercised before permitting such patients to be operated upon

It is well known that the posture of the patient is often a gross index to his emotional attitude He reflects, in the way he carries himself, the attitude that he has toward himself and the world The dejected (depressed) patient shows his dejection in his posture, and the confident, secure patient often reflects his attitude in the erect way that he carries himself

If we listen as carefully to what people say as to the sounds that their hearts make, we will often find that they express their problems in symbolic language Again and again we find these patients "burned-up" with resentment and "aching" to express their unappeased hostility I do not know the cause of the slight fever in such cases but I do not look upon it as significant Reimann's study[4] of the problem of long-continued low-grade fever concerned sixteen women In them he found a high incidence of neurosis He concluded that a certain proportion of normal individuals have temperatures regulated at levels slightly higher than 98 6° F and that temperature of these levels is often found in neurotic persons

This leads me to a consideration of "constitutional inadequacy," which I look upon as a very unfortunate term Most of these patients are not constitutionally inadequate We must distinguish between pseudoheredity and pure heredity If we look to the environment to the family group especially, for the origin of these psychosomatic disturbances, we will often find emotional conflicts, by bringing the material to the surface and dealing with it in a more realistic way we can sometimes help these patients to become useful citizens again instead of labelling them constitutionally inadequate or burdening them with that other equally unsatisfactory term neurocirculatory asthenia, which is usually just a name to cloak our ignorance of the life situation of the individual

The same strictures apply to the various symptom diagnoses that are often made in the study of these patients and to which too much attention is paid increasing the anxiety of the patient In other words, the physician often becomes a pathogenic agent when he approaches these patients purely from an organic standpoint and stresses insignificant physical or physiologic deviations

Probably the most difficult problem at the present moment is the question of chronic brucellosis (We are warned again and again that we must not make a diagnosis of neurasthenia, which under such circumstances is a psychologic term without psychic meaning until we have ruled out the possibility of chronic brucellosis) It is true that chronic brucellosis produces a clinical picture not unlike the one we are describing but in the first place we ought to be able to establish that diagnosis with some certainty and without too much delay and secondly we must not forget as Harris[5] points out, that the two disorders—brucellosis and specific forms of psycho-

neurosis—may coexist In this connection I would like to say that the emotions often exploit an organic illness and thus it is that frequently, in connection with an infectious disease or after operation, convalescence lingers and invalidism sets in The belief is widespread that *the organic disease* produced the neurosis, whereas the actual mechanism is that the organic process has broken down the individual's psychologic defenses, regression occurs, and the patient's predisposition, determined by his personality structure, permits the neurosis to emerge.

A contrary aspect of the relation of organic disease to neurosis is the severe neurotic disorder—hypochondriasis, for example—in which the patient is obsessed with his neurotic symptoms and inattentive to some serious disorder I have frequently observed that the patient who insists "that his *illness is physical" is apt to be suffering from a disorder of emotional origin,* while the patient who is eager to blame it on the psyche often has an organic disease

[illegible] medicine refers to the structural an [illegible] the underlying or associated psych[illegible] int of the physician-patient relationship it is important to know whether the symptoms are on the basis of conversion hysteria or are a part of the clinical picture of depression in which the mood disturbance is overshadowed by the somatic complaints. When one deals with depression there is often the threat of suicide [illegible]

position for comprehensive medical care.

In addition to the term psychogenic rheumatism, we must add the psychiatric diagnosis applicable to each case because it is the psychopathology that is chiefly responsible for the syndrome and it is by means of psychotherapy that we can deal with these patients most effectively.

TREATMENT

In approaching the patient from the standpoint of psychosomatic diagnosis one must realize that in dealing with the emotions one cannot separate treatment from diagnosis and that really as soon as one has made an initial contact with the patient the groundwork is being prepared for treatment. There can be no sharp division between the period of diagnosis and the period of beginning treatment

I would urge that the physical aspects of the study be completed as quickly as possible. This applies especially to brucellosis, *which is a particularly* vexatious problem at the moment, one reason being that so many patients get skin-tested that the tests themselves induce immune reactions resulting in low titer agglutination responses

I would also urge, once we have satisfied ourselves that the slight temperature elevation is only an insignificant phase of the disorder, that instead of suggesting to these patients that they keep a record of their temperature we tell them to stop taking it They must stop being slaves to the thermometer.

Once we have excluded physical disease and done it expeditiously we can say to these patients that they have no evidence of organic disease, adding, in particular that there is no evidence of arthritis and that they

will not be crippled by that disease Often it is wise to add at a later point that neither do they have evidence of mental disease, because so often, with lay misconceptions regarding emotional problems, to suggest that the disorder is emotional means to the patient that it is mental and that he may be in danger of "losing his mind"

I always ask the patient toward the end of the study, "What have you thought about the cause of your illness?" We will often be amazed at the extraordinary ideas that these patients have had, some of which they have obtained from their reading or fantasies and some of which have been supplied by the many medical examinations and investigations that have been done We can make no headway with these patients from a treatment standpoint until we have these first layers of anxiety out on the surface. It is like the layers of an onion, as they are peeled off, new problems present themselves and these new problems will usually be found within the family group Marital incompatibility and sexual difficulties are almost always present but the patients often hesitate to discuss them because they regard them as personal problems unrelated to their illness

When we say to these people that their aches and pains and fatigue are due to the fact that they are always in a state of tension, that they do not know how to relax, even at night, and that because they are taut their muscles are crying out in protest with aches and pains, it carries conviction and provides a stepping stone for them to begin to talk about their emotional problems When pains persist or recur one may sometimes make the suggestion that, after all, emotional immaturity is the background of a psychosomatic disorder and that "growing pains" that occur later in life are apt to be more painful than when they occur early in life

Chronic resentment—smoldering discontent—is the special emotional problem in these patients but it had better be approached indirectly One must avoid the crude suggestion that they are angry at someone who is supposed to be near and dear to them or
filial respect That problem can be
patient aware of the discontent and
study his day-to-day existence and r
to the point where symptoms appear. We must let the patients see that they are suffering not from disease of body or mind but rather from a disorder of their feelings

Instead of cautioning rest and more rest, which only permits these people to "stew in their own juices," I recommend that they "carry on in spite of symptoms," and this they will often be able to do once they have divorced their pain from the fear of arthritis, heart disease, cancer or what not Once neurotic pain is divorced from a fear of organic disease, it is remarkable how rapidly it will disappear or diminish At the same time I recommend that they do not talk about their illness to their friends but try to cultivate the atmosphere of health by telling people that they are well no

they are being used in a supplementary capacity and that the cure lies in emotional reeducation It is of course sometimes necessary to make certain concessions to the previous organic miseducation that the patient has had We cannot go too quickly in changing our approach from disease to

disorder, from the idea of doing something for the patient to having him do something for himself, from education along physical lines to the necessity for emotional growth Many of these patients are emotionally quite ill and the efforts of the physician untrained in psychopathology to elicit material of importance will not only fail but may prove harmful The essence of psychotherapy, some knowledge of which should be a part of the equipment of every physician, is to go no faster than the patient is prepared to go.

In connection with physical medicine I think one more word ought to be said and that concerns the problem of belts, braces and supports So often we find these patients wearing sacroiliac or abdominal supports when what they need is inner support. Instead of trying to bolster them up with a crutch what we ought to do is try to develop their inner, emotional security so that they won't have to lean on supports, or braces, or for that matter on their physician

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DISCUSSION

FRANCIS J BACH

A century ago, the family doctor and the patient's relatives, and possibly the lady of the manor, dealt with the social and economic problems as well as the physical ills of the village craftsman when he fell sick The doctor combined in himself a knowledge of the personalities of his patients and, often literally from birth, of their mode of life, of their habits and, not infrequently, of their problems and worries He knew his man, not only the disease This has altered Today, the patient is probably one of a thousand working in a factory many miles from his home, and the status of his doctor has altered, partly because of these environmental factors and partly because of the development of elaborate diagnostic procedures, clinical, laboratory and psychologic, which have led to increasing specialization That these specialties have their own language is obvious to those who read the studies on arthritis in journals such as *Psychosomatic Medicine* and the biochemical reviews

As a reaction against this over-specialization, there is a move toward a

return to a holistic approach to the patient, an assessment of the patient as a whole based on morphologic, physiologic and psychologic characteristics This is "constitutional medicine" of which one of the great pioneers was Dr. George Draper. It has, in part, been systematized by Dr Sheldon and others, and the psychosomatic aspects have been brought vividly to our notice by the important studies of Dr Weiss

Those of us who are interested in the study of rheumatic diseases need training in both psychopathology and general medicine When the teaching of the principles and the proven tenets of psychosomatic medicine have become an integral part of medical education, then the doctor will again be able to study his patient as a whole At present it is even harder for many of us to understand the language of the psychiatrist than to appreciate that of the biochemist and morbid anatomist

May I, with diffidence, suggest that for study we take Wittkower's classification and group our clinical problems, especially our rheumatic problems, under three headings The first group includes disorders, be they "functional" or "organic," in the etiology of which psychologic factors are directly relevant in combination with other causes Recognized examples of these are conditions such as nervous dyspepsia and peptic ulcer. I would add rheumatoid arthritis and, possibly, what we have had described as 'psychogenic rheumatism" In the second group are disorders in which the causation has been established as being due to physical factors such as infection, but in which psychologic factors indirectly play a precipitating or predisposing role Syphilis, gonorrhea and tuberculosis may be included in this group, and these are all known causes of arthritis The third group comprises disabilities in the etiology of which psychologic factors play no part, and which are of such a nature as to cause severe emotional disturbance in the individual concerned I would only mention disablement due to war injuries such as paraplegia, and possibly severe degenerative joint disease or osteoarthritis which has led to crippling of long duration

For many years I have believed and taught that rheumatoid arthritis is a psychosomatic syndrome, in which metabolic and psychologic factors appear to play a more important role than does so-called infection And I have stressed the part that endocrine dysfunction may play in its causation I do not believe that a happy and contented person will develop this disorder My own studies in the hospital with the social worker or the almoner, and in private practice especially during the early years of the war, have convinced me that the people who get rheumatoid arthritis and possibly certain forms of fibrositis are of certain constitutional types, with typical personality and physical characteristics Chronic frustration, anxiety and shock came out so often in a carefully taken clinical and social history

To review the natural history of rheumatology There was the initial phase of "diathesis" and the study and treatment of the whole man, then, early in the century, there was the "surgical" phase of so-called "focal" infection and of its treatment by drastic eradication, then the "medical" phase, with less severe methods of treatment by so-called reticulo-endothelial stimulation with metal such as gold and with vaccines, and now there is the "mechanical" phase of endocrine disturbance and its reversibility. This is a magnificent and dramatic advance for which we owe much to Dr Hench and his co-workers, Drs Kendall, Slocumb and Polley

Psychosomatic or constitutional medicine combines what is best in the old and the new, and I look forward with pleasure to the next phase in rheumatology, when it will take the lead.

Accepting, as we should, the essentially objective criteria for the clinical assessment of therapeutic methods as adopted by the American Rheumatism Association, it is my opinion that as a method of treatment, the regulation of endocrine disturbance alone will stand up to these clinical criteria. We have a long way to go and we clinicians and psychiatrists, possibly with the help of the physiatrist, can and should work in close cooperation so as to contribute to this subject work of even greater value than that of the clinician and pathologist of half a century ago and of the clinician and biochemist of today.

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ABSTRACT

DISEASES ARISING FROM OVERSTRAIN AND WEAR AND TEAR ON THE MUSCLES OF THE SKELETAL SYSTEM, OFTEN CONCEALED BEHIND THE DIAGNOSES OF NEUROSIS AND RHEUMATISM

HENRIK SEYFFARTH AND KIRSTEN MØINICHEN

In skeletal disease and also in disorders of tendon attachments the tendency to produce referred pain is far greater than in the primary myoses, where the pain is chiefly located in the vicinity of the most tender muscles. Palpation of the tender muscle reveals so-called myosis, "a voluminous, doughlike, mostly inelastic, not sharply delimited part of the muscle" (Helweg). The diagnosis "psychically conditioned pains" is usually an indication of the physician's inability to detect the organic cause of the pain The primary myoses (functional myoses), due to hyperfunction of muscles, are differentiated from secondary myoses, which arise in connection with a medical, neurologic, or surgical disease

Special investigation of the musculoskeletal system consists of complete anamnesis and physical examination, including psychic status, motor function, sensibility, coordination, and reflexes

Emotional or affective pain occurs because emotions normally increase pain and feeling of fatigue and induce muscular tension, which in itself may call forth pain in tender muscles, tendon attachments and joints Anxiety tension finds expression mainly in a fixation of the thorax in the inspiration position with drawn-up shoulders

The best treatment for neuroses has proved to be relaxation gymnastics, to teach the patient to relax during work and to release the fixed mechanism of respiration By such daily gymnastic exercises and training in the proper manner of working, with least possible tension, it has been found possible practically to eradicate functional diseases in the musculoskeletal system as a cause of industrial absenteeism, whereas in 1944, 25 per cent of the absenteeism was due to overstraining the neck and arms

OSTEOARTHRITIS

DIAGNOSIS OF OSTEOARTHRITIS

AUGUSTUS M. DAVISON

The criteria for making a diagnosis of osteoarthritis vary Physicians often disagree in a given case, especially where compensation is involved, as to whether such a diagnosis is justified and whether it is the true basis of the alleged symptoms Some resign themselves to the diagnosis once the roentgenogram reveals the least hypertrophic reaction, whether symptoms are present or not. It is remarkable that the oldest disease known to man is as yet so imperfectly defined I propose to offer a practical answer to the query, "When shall a patient be said to have osteoarthritis?"

Hench and others have admonished against the casual application of the term arthritis to patients lacking intra-articular disease, and have pleaded for more discrimination in its use. "The implications contained in the word are such that it is not a designation to bandy about promiscuously. To all *but the most phlegmatic patient it comes as a prophecy of real trouble* ahead, a threat of long illness and perhaps of slow, painful retirement "[1]

To many patients labeled osteoarthritic, there is surprisingly little comfort in the physician's reassurance that this is a localized and relatively benign condition In general, therefore, it is undesirable to brand a patient with arthritis without proper indications

Ivy has drawn attention to the degenerative diseases, including osteoarthritis, which maim aging persons prematurely "It is rational to distinguish between the degenerative diseases and the processes, retrogressive or degenerative, which occur as a natural concomitant of life "[2] It is desir- [illegible] the joints [illegible] estrict the [illegible] Diseases [illegible]

The cause must be unknown Let us therefore exclude those conditions of similar roentgenographic appearance which are clearly secondary to trauma, to improper weight bearing or to structural defects, and place these in separate categories of traumatic arthritis, congenital malformation, deformity and other appropriate diagnostic terms

Of predisposing factors, only heredity has stood the test of inquiry. Climate, trauma, menopause and old age are usually only coincidental[3]

PATHOLOGY

Our first assumption, then, is an unknown etiology Next let us accept the pathologic process as primarily a degeneration of articular cartilage by fibrillation, splitting, pitting, softening, yellowing and irregular thinning[4] The appearance of these changes in the knees as early as fifteen years of age has been described,[5] and others have agreed that it is common in the third decade, but, of course, no symptoms are encountered at this early stage The appearance of marginal proliferation follows by years Also characteristic is the later appearance of osteosclerosis adjacent to the affected joint cartilages

CLINICAL CHARACTERISTICS

The clinical characteristics fit the pathologic process. The onset is invariably gradual. There is a lack of acute inflammation There is no pain at rest, but only with use. Coarse crepitus usually can be felt. Soft tissue swelling is not a conspicuous feature Adhesions do not form. Motion may be mechanically limited at the extremes but is not lost in ankylosis The roentgenogram reveals thinning of cartilage, osteosclerosis and osteophytes as soon as sufficient derangement develops to produce symptoms, and usually long before

There are only two symptoms, pain and limitation of motion Pain varies from mild to moderate, is rarely severe It is proportionate to the use of the joint, hence characteristically most pronounced in the evening and after unusual activities It is alleviated by rest We need not settle the explanation of the invariable remissions and exacerbations of pain as yet, for the mechanism producing pain is still speculative While varying in degree, however, it may not vary in location for the symptoms are quite localized

The degree of limitation of motion is also mild and occasionally moderate. Limitation may be more marked at times of most pain through protective muscle spasm It is rare that joint destruction proceeds to such extent as to forfeit all motion

On this working hypothesis, let us base certain arbitrary conclusions How does one arrive at a justified diagnosis? It is preferable to eliminate the bulk of elderly persons with presymptomatic roentgenographic changes, else most people past fifty would be labeled as diseased when in fact they are quite conformative to the norm Hence two prerequisites to diagnosis must be met, an accep
graphic confirmation o
may not be confirmed
diagnosis of any joint
genologist the diagnostician and mocks the judgment of the clinician Hypertrophic bone reaction is not synonymous with the clinical disease osteoarthritis.

NONDIAGNOSTIC FINDINGS

A common error is to offer a diagnosis of generalized osteoarthritis Actually there is no such condition Idiopathic osteoarthritis is practically never encountered beyond a certain few joints, namely the distal and proximal interphalangeal joints of the fingers, the carpometacarpal joint of the thumb, the acromioclavicular joint, the lower four cervical vertebrae, the lumbar vertebrae, the lumbosacral joint, the hip and the knee No patient exhibits all these possibilities, usually only one or two localities are involved. Osteoarthritis is purely a local condition, and only the proven joints are acceptable in the final diagnosis

Systemic manifestations such as anorexia, fever, weight loss, abnormal fatigue, anemia and elevated sedimentation rate are not characteristic Accepting inappropriate symptoms as related to incidental hypertrophic findings on roentgenography is fallacious Generalized fatigue is indicative of an infection, systemic disease, neurosis, etc , but can never be attributed to osteoarthritis Radiculitis is commonly described in osteoarthritis of the spine, but is rarely encountered in the author's experience Vague but severe

incapacity of largely subjective nature, and clearly psychogenic, has nevertheless been attributed to a few innocent spurs in many patients

Crepitus, though not considered normal, does not of itself warrant a diagnosis of osteoarthritis [3] It occurs in several other conditions as well as in persons without recognizable disease.

CONCLUSION

Out of the wealth of clinical knowledge before us, certain established features of osteoarthritis have thus been woven into a practical concept of the disease, a prerequisite to proper treatment and disposition of such patients People demonstrating physiologic aging of the joints do not merit a label of disease The appellation osteoarthritis is preferably reserved for those persons demonstrating symptomatic and pathologic (excessive or premature) degenerative disease

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THE PATHOLOGIC DISTINCTION BETWEEN OSTEOARTHRITIS AND OSTEOPHYTOSIS OF THE SPINE

DOUGLAS H COLLINS

This communication presents no fundamentally new knowledge of the pathologic conditions affecting the vertebral column but only modifications of views formerly expressed by other morbid anatomists I consider that a re-presentation of the subject is not out of place because physicians generally continue to refer to osteoarthritis or hypertrophic arthritis of the spine without distinguishing between two unrelated morbid conditions which may very well be associated with two distinct clinical syndromes

OSTEOARTHRITIS

Recent work on osteoarthritis of limb joints now enables us to define this disease in precise pathologic terms It is a disease of synovial (diarthrodial) joints, beginning with injury or degeneration of hyaline articular cartilage and leading through a series of elaborate progressive changes to the state in which the bone ends are altered in shape and form, denuded of cartilage and surrounded by shelves and spurs of new osteophytic bone It is most desirable that the term "osteoarthritis" should be reserved specifically for this disease which, by definition, only affects the diarthrodial joints

The earliest stages of osteoarthritis are not detectable either radiologically or by the examination of macerated anatomic specimens, both of which

reveal only the later stages when marginal hyperplasia *of bone has occurred.* Evidence is not lacking from publications of other authors, who have used one or other *of these techniques,* that true osteoarthritis not uncommonly affects the synovial (apophysial and costovertebral) *joints of* the spine. A few, by patient dissection of fresh specimens, have been able to show the early stages of cartilage fibrillation and erosion in these joints I have found osteoarthritic cartilage changes quite frequently in the apophysial (but rarely in the costovertebral) joints of the spines of elderly subjects. The distribution of the lesions through the vertebral column seems to be irregular. In these cases we have the condition which can truly be called spinal osteoarthritis Its clinical correlations are bound to be difficult to determine, but it is important to be aware of the existence of such a condition.

OSTEOPHYTOSIS

Spinal osteoarthritis may exist, and usually does exist, without the presence of marginal lipping of the vertebral bodies. This latter feature characterizes spinal osteophytosis and results from an entirely different pathogenic mechanism As long ago as 1897, Benecke connected it with a disorder of the intervertebral disk, and subsequent work by Schmorl (who called the condition of multiple osteophytes "spondylosis deformans") and by others more recently has amply confirmed this view.

Osteophytes cannot form so long as the nucleus of the intervening disk is intact and the vertebral bodies are normally separated Collapse of the disk, however, through degeneration or prolapse of the nucleus, leads to slight forward tilting of the vertebrae and the forward extrusion of what plastic disk substance remains It is on either side of this extruded disk substance that the osteophytes subsequently develop The common place for osteophytes is in an anterolateral position just to one side (usually the right-hand side) of the anterior common ligament, whose strong attachments are sufficient to prevent the extrusion of the disk in the mid-line anteriorly In a scoliotic spine the disk extrusions and the osteophytes form in the concavities of the spinal curve where the vertebral bodies are tilted laterally towards one another.

Disk collapse and osteophytosis of the vertebral bodies soon leads to immobilization of the affected spinal segments. There is no reason, therefore, to think that osteoarthritis of the apophysial joints will follow

In senile kyphosis, where the disks, as they degenerate, are vascularized and often partially ossified, there is no extrusion of disk tissue and no osteophytes form But where the disk collapses while it is still plastic, it may bulge forward and lead to osteophyte growth

Further evidence of the discogenic origin of osteophytes is obtained in the records of the experimental puncture of disks in animals and the accidental puncture of disks in man

It is a common experience that spinal osteophytosis is discovered accidentally by roentgenography or at autopsy and that it seems to have little clinical significance. I think it is much less likely than spinal osteoarthritis to cause pain from movement and protective muscle spasm, since the tendency is to anatomic fixation of the part. Disability may arise, where a number of successive vertebrae are grossly osteophytic, from rigidity of a consider-

able section of the spinal column Segmental neuritis has been ascribed to distortion of the foramina in cases with localized osteophytosis but it is possible that this symptom might be due to intraspinal prolapse of nucleus pulposus, since this lesion is also in some cases followed by the appearance of anterolateral osteophytes.

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ABSTRACTS

"RHEUMATIC" SYMPTOMS ARISING FROM THE CERVICAL SPINE, AND THEIR TREATMENT

JOHN MCM MENNELL

Any bodily ache or pain which is presumably not visceral and is chiefly subjective tends to be diagnosed as rheumatism, including pains in the head, neck and shoulders Some of these symptoms may arise from impaired function of the interlaminar joints in the cervical spine Treatment—namely, manipulation—directed at restoring normal movement to these joints will relieve symptoms

Adequate clinical examination to infer impairment of joint function requires a full understanding of the anatomy and physiology of joint movement The normal range of joint movement is made up of a normal voluntary range and normal involuntary range Once a clinical inference of loss of joint function is made, then restoration of function by manipulation is the logical treatment. If movement in the normal involuntary range is impaired, only movement by manipulation can restore it, and until it is restored, normal voluntary movement must remain impaired. The art of manipulation lies in the accurate knowledge of the normal involuntary range of movement

One must recognize that joint dysfunction gives rise to distant symptoms, i e, referred pain. Pain from the interlaminar joints in the cervical spine can be referred along the distribution of any of the cervical nerves The sympathetic nervous system almost certainly plays a part in the production of referred pain.

THE CERVICAL SYNDROME RELATION OF THE PAINFUL SHOULDER AND BRACHIALGIA TO OSTEOARTHRITIS OF THE CERVICAL SPINE AND "PERISPONDYLITIS CERVICALIS"

P VAN DER MEER

changes were frequent, and special attention is drawn to changes in the uncovertebral joints. However, roentgenographic changes were often inadequate to account for the observed symptoms and course of this syndrome. The involvement of soft tissue structures around the spine as a (possibly rheumatic) perispondylitis is advanced as an explanation of the discrepancy between clinical and radiologic findings. This concept is also important with respect to response to treatment.

THE EFFECT OF CORTISONE AND OF ACTH ON RHEUMATOID ARTHRITIS AND ACUTE RHEUMATIC FEVER*

PHILIP S HENCH, EDWARD C KENDALL, CHARLES H. SLOCUMB AND HOWARD F POLLEY

We have administered the adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (Kendall's compound E) to twenty-one patients and pituitary ACTH to six patients with severe or moderately severe rheumatoid arthritis In each case improvement in clinical features and reduction of sedimentation rates occurred within a few days This improvement generally disappeared promptly when administration of either hormone was discontinued

The rarity of these compounds and the limited scope of our preliminary data (especially regarding prolonged administration) make inappropriate now the use of the term "treatment" except in an investigative sense This paper is presented, not as a clinicotherapeutic report, but as a study of certain physiologic effects which these new hormones exert on rheumatoid arthritis and certain other diseases

ANTECEDENT CLINICAL WORK

[illegible]

every rheumatoid patient corrective forces lie dormant, awaiting proper stimulation It was concluded that rheumatoid arthritis was not necessarily a relentlessly progressive uncontrollable disease for which no really satisfactory and rapid method of control need ever be expected Regardless of the supposed validity of the microbic theory the disease obviously could be profoundly influenced by a phenomenon which was primarily biochemical.

The dominant feature of jaundice suggested at first that the unknown ameliorating agent, to which was given the name "antirheumatic substance X," was a hepatic or biliary constituent Hepatic substances and procedures were applied without much success[7] These procedures included the administration of various biliary products, the production of experimental hyperbilirubinemia, transfusion of blood from jaundiced donors and the induction of jaundice by means of toluenediamine, icterogenic serum or lactophenin The last two agents produced articular remissions but the mechanism of relief was not apparent

Meanwhile, between 1931 and 1938 the beneficial effect of pregnancy

* The number of cases mentioned and much of this report is given here as it was presented at the Congress (Seventh International Congress on Rheumatic Diseases on May 31, 1949), but later parts of the report have been brought up to date by the inclusion of certain data obtained since the Congress

on rheumatoid arthritis was also being studied.[8] In view of the phenomenon of relief of the disease by jaundice or pregnancy the further pursuit of evidence *in support of the microbic theory of rheumatoid arthritis* seemed less attractive than an investigation of the nature of substance X It was conjectured that rheumatoid arthritis involved some basic biochemical disturbance which is transiently corrected by some incidental biologic change common to a number of apparently unrelated events.

It seemed logical to suppose that what causes relief of rheumatoid arthritis in pregnancy is closely related to, if not identical with, that which relieves the same disease in jaundice. It could be neither bilirubin nor a unisexual hormone, because jaundiced rheumatoid men obtained the same relief as pregnant rheumatoid women without jaundice The belief was stated that some biochemical denominator common to jaundice and pregnancy might provide us with an improved treatment or control of the disease.

It was conjectured that the hypothetic substance X was not a disintegration product from a damaged liver but probably was a biologic compound specific in nature and function, one which was normal to the human organism and of which, perhaps, the arthritic patient did not have enough Since pregnancy alters the concentration of hormones, substance X might be a *bisexual steroid hormone, perhaps an adrenal hormone.* Temporary remissions of rheumatoid arthritis are frequently induced by procedures capable of stimulating the adrenal cortices, such as general anesthesia, surgical operations or starvation In 1938 we administered to several rheumatoid volunteers, lecithin from the adrenal gland in an attempt to induce hyperlipemia such as may occur in association with pregnancy and jaundice Among other substances which came under our consideration in 1938 we listed whole adrenal cortex extract, then called "cortin," but we did not use it until later

Prior to 1938 substance X was regarded only as an antirheumatic Then it was noted that pregnancy or jaundice sometimes relieved temporarily such nonrheumatic or allergic conditions as hay fever, asthma, sensitivity to eggs, migraine and psoriasis Hence it was suggested that substance X was antiallergic as well as antirheumatic, and that the phenomenon of relief was not disease specific but was group specific. This lent impetus to the study because *it was now suspected that if substance X could be identified* it would be useful against a number of diseases. In an attempt to identify

try compound E whenever it might become available

ANTECEDENT CHEMICAL WORK

The early chemical studies were carried out independently from *1930* to 1938 by Reichstein and his associates[9] in Switzerland, and by Wintersteiner and Pfiffner,[10] and Kendall and his associates[11-16] in this country Each group made contributions to the isolation and chemical formulation of the group of steroids elaborated by the adrenal cortex.

The task of partial synthesis of these compounds was begun in 1940 A small amount of dehydrocorticosterone (compound A) was prepared in *1944 in the laboratories* of the Mayo Foundation, a larger sample was pre-

pared by the same method by Merck & Co, Inc in 1945 But compound A was found[17] to be of little value in Addison's disease, this was a great disappointment

Some time previously compound E had been found by Ingle to have a marked effect on muscular activity.[18, 19] It was now decided to attempt to produce compound E by partial synthesis A few milligrams of compound E were first prepared by Dr L H. Sarett in the research laboratories of Merck & Co, Inc, in 1946, but the method which he used was not suitable for large-scale production After continued effort on the part of Kendall and his associates in the Mayo Foundation and the chemists in the research laboratories of Merck & Co, Inc, compound E acetate became available for clinical testing in May, 1948, and was given thereafter with satisfactory results to a few patients who had Addison's disease.[20-22]

CORTISONE (COMPOUND E) FOR RHEUMATOID ARTHRITIS

In August, 1948, we decided to try compound E if it was available A letter requesting sufficient compound E for one patient was sent to Merck & Co, Inc, September 4, 1948 The letter concluded: "We know that there is a potentially provokable mechanism [for the reversibility of rheumatoid arthritis] which is activated by pregnancy and jaundice very rapidly, by jaundice for example within 3 days . . . Therefore if any adrenal compound is of real significance in rheumatoid arthritis we would expect to see some results within a very few days" A small supply of compound E was obtained* and first administered to the patient on September 21, 1948[23, 24]

Preparation and Dosage Between September, 1948, and January 19, 1949, we used free compound E (Merck), which we have renamed cortisone, since then we have used cortisone acetate (compound E acetate) Of cortisone, 100 mg was usually injected intragluteally each day. Of cortisone acetate, 300 mg. was usually given intragluteally the first day and 100 mg daily thereafter. Under special circumstances 150 to 200 mg has been given daily for about two to four weeks Smaller daily doses of 25 to 50 mg were found to be inadequate in these severe cases A single daily dose of 100 mg appeared to be as effective as multiple smaller doses.

To May, 1949, cortisone had been given for short periods of from eight to sixty-one days to sixteen patients and for longer periods, that is, more or less continuously for from four to nine months, to five patients

Controls To provide adequate controls the use of cortisone was in some cases preceded, in other cases replaced, by the use of a suspension of cholesterol similar in appearance to cortisone or cortisone acetate The times when the control solution and the adrenal hormone were interchanged were always unknown to the patients and were for five weeks unknown to the three clinicians evaluating the results

Initial Clinical Effects on Muscles and Joints In each of the 21 cases a pattern of improvement was evident Usually, the fibrositic component (muscular and articular stiffness) began to diminish within the first twenty-four or forty-eight hours after use of the hormone was begun, and often was markedly or completely relieved within a few days Second, articular

* Through the courtesy of Dr Randolph Major, Vice-President, and Dr James M Carlisle, Medical Director, Merck & Co, Inc

17-KETOSTEROIDS.* Urinary concentrations, which usually were in the low normal range, were reduced by use of cortisone, then increased, but remained in the low normal and even subnormal range.[25, 26]

CORTICOSTEROIDS.* The excretion of corticosteroids in the urine always increased when cortisone was used. Usually a peak of a few milligrams (not more than 5) was excreted for twenty-four hours, which was followed by a decline to a fairly constant level between 1 and 2 mg.[25, 26]

HEMOGLOBIN. In several cases concentrations of hemoglobin increased during the use of cortisone Representative increases were. 2 7 gm in sixty-four days and 3 gm in 215 days In 1 case hemoglobin increased 1 4 gm during the first (sixty-day) course, 1 4 gm. during the second (eighty-five-day) course and 1.9 gm during the third (seventy-three-day) course of cortisone.

When the use of the hormone was discontinued, the concentration of hemoglobin often decreased.

ERYTHROCYTES Erythrocyte counts often increased somewhat, from a few to several hundred thousand cells per cubic millimeter, within a few weeks

LEUKOCYTES. In certain patients an increase in the total number of circulating leukocytes and immature granulocytes, and lymphopenia occurred

ACTH FOR RHEUMATOID ARTHRITIS

The first relatively pure pituitary adrenocorticotropic hormone was prepared in 1933 by Collip, Anderson and Thompson In 1942 further purification was accomplished by Li, Simpson and Evans[27, 28] and by Sayers, White and Long[29, 30] Because of the scarcity of material between 1943 and 1948, only a few clinical studies were made on normal subjects and patients with obvious endocrine defects, chiefly patients with adrenal insufficiency.[31–35]

Having noted the effect of cortisone on rheumatoid arthritis, we considered it logical to determine the effect of ACTH, which stimulates responsive adrenals to produce cortisone or the cortisone-like substance, compound F. But we were not able to use ACTH until February, 1949. Before giving it, we were not certain what our results would be If the adrenal glands of rheumatoid patients were producing, not cortisone, but an altered product related to the cause of the disease, stimulation of such adrenal glands might increase rather than decrease articular symptoms But this uncertainty was resolved when we observed in February, 1949, that ACTH produced essentially the same antirheumatic effect as cortisone did

Preparation and Dosage We have used ACTH given to us through the courtesy of Dr John R. Mote, Director of Medical Research, *The Armour* Laboratories The potency of different lots varied somewhat We generally have given 100 mg daily, occasionally the dose has been 45 to 140 mg Fairly large doses should be used at first until the disease is largely suppressed; thereafter smaller doses may suffice Since ACTH is rapidly utilized by the body, the total daily dose must be given in divided doses, at first every six or eight hours, later perhaps an injection twice a day may suffice The pituitary hormone was given daily for eleven or twelve days.†

[illegible] for determination of the

[illegible] given ACTH to other

Clinical Effects. The immediate response to ACTH in each of our six cases of rheumatoid arthritis was similar to that from cortisone: a diminution [illegible] The maximum [illegible] which time [illegible] continued further improvement occurred slowly Increased appetite and weight resulted from the use of ACTH as from cortisone [illegible] and markedly, an[illegible] cre[illegible] to six days after ACTH was given Serum globulin and total proteins decreased slightly, the concentration of albumin in serum was not significently altered, albumin/globulin ratios increased slightly Concentrations of 17-ketosteroids and corticosteroids in urine increased promptly and markedly

EFFECTS OF CORTISONE AND ACTH ON SYNOVIAL HISTOPATHOLOGY OF RHEUMATOID ARTHRITIS

Articular biopsies of synovia of the knee were carried out in several cases before and at various times during the use of cortisone or ACTH for rheumatoid arthritis. In each case synovial inflammation appears to have been reduced by these hormones as indicated by reduction in the cellular reaction with a decreased number of plasma cells and lymphocytes, reduction of papillary tufting, reduction or absence of deposition of fibrin and lessened necrosis and edema [25]

DATA ON CORTISONE AND ACTH

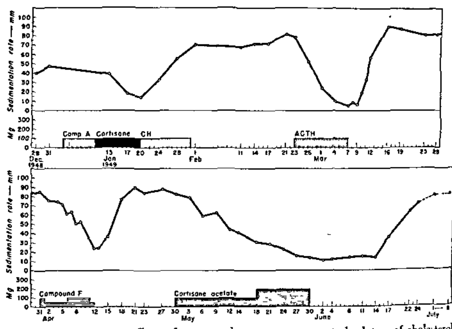
Comparative Dosage ACTH and cortisone (preparations of 1948 and 1949) are not physiologically equal, milligram for milligram One hundred milligrams of ACTH apparently stimulates the production of more than the equivalent of 100 mg of cortisone, possibly 200 mg or even more Therefore 40 or 50 mg of ACTH may be as effective as 100 mg or more of cortisone. The newer (1950) preparations of ACTH are more potent, the ratio of their potency to cortisone has not been established definitely This distinction as to relative dosage will explain most of the clinical and biochemical differences between the results obtained from the two hormones

Comparative Effects on Sedimentation Rates These were reduced more promptly by 100 mg of ACTH than by 100 mg of cortisone (Fig 12). *Rates increased more promptly after withdrawal of ACTH than after withdrawal* of cortisone [25]

Other Comparisons Because ACTH is more rapidly absorbed and metabolized, it must be given oftener (two to four times daily) than cortisone (generally once daily) The adrenal glands of most, but not all, patients with rheumatoid arthritis are responsive to ACTH [36] But patients whose adrenal glands are not responsive to ACTH (as shown for example by Thorn's test[37] or by increases of urinary steroids) should derive little or no benefit from ACTH though they may be helped by cortisone

Effects Related to Toxicity or to Unsatisfactory Preparations Rarely a short febrile reaction accompanied a given injection of cortisone, this perhaps was due to pyrogens in a particular bottle Derived from pituitary

glands of pigs or horses, ACTH is to man a foreign protein. Fever and hives developed in 1 case after two of five injections of ACTH given to test adrenal function during the use of cortisone. Cortisone, not being a protein, did not produce any such reaction



. . . of cholesterol

similar amounts of cortisone

SIDE EFFECTS

Definition Cortisone and ACTH are powerful agents which may affect many bodily functions and many tissues other than those of joints and muscles During our further experiences we have observed a number of effects other than the dominant antirheumatic one.[25, 26] The desirable ones should not unthinkingly be called "clinical effects" and the undesirable ones "side effects" They are all physiologic effects But the term "side effects" is widely used by investigators in this field, and since its meaning appears to be well understood we will use it for the present.

Incidence About 75 per cent of our patients who were given cortisone or ACTH for from a few days to a few months for rheumatoid arthritis showed either no or mild side effects. Moderate or marked side effects occurred in the remaining 25 per cent In general the significant side effects

nones in what we now believe

cortisone or 100 mg of ACTH

00 mg of cortisone, for relatively long periods Although dosage and length of administration were the two chief factors which governed the development of side effects, in-

dividual tolerance also played a role Men tolerated either hormone better than women, especially menopausal women [25]

Grouping and General Incidence. A physiologic grouping of these side effects has been presented elsewhere [25, 26] The commoner side effects consisted of certain paresthesias or somatic symptoms somewhat resembling those considered "functional" There was a tendency for an initial retention, then sooner or later a liberation, of salt and water and reduction of serum potassium; in only one case was the latter severe Cortisone in doses of 100 mg daily usually induced no significant alterations in the plasma electrolytes. However, daily doses of 200 mg of cortisone or of 100 mg of ACTH sometimes produced a negative nitrogen balance and a transient hypopotassemic, hypochloremic alkalosis which was usually mild and symptomless, but occasionally was marked and produced symptoms.[25, 26]

In any patient with latent or frank diabetes these hormones should be expected to produce transient reduction of carbohydrate tolerance [20, 21, 26, 38, 40] No marked impairment of carbohydrate tolerance occurred among our rheumatoid patients although cortisone or ACTH often was given for prolonged periods.[26]

The effects of hypercortisonism (resembling those seen in Cushing's syndrome) noted were rounded face in seven cases, mild hirsutism in seven cases, weakness and lassitude in seven, transient reduction of libido in three males, mild acne in two, and amenorrhea or striae in one case each Minor alterations of psyche (euphoria, mild nervousness) often occurred, depression developed in one case.

These side effects have been transient and reversible

Measures to Prevent or Control Side Effects Our attempts to do this have met with limited success Retention of salt and water can usually be prevented or controlled by limiting the patient's intake of salt or, if necessary, giving potassium chloride or a mercurial diuretic The intermittent use of estrone during administration of cortisone appeared to prevent most of the side effects which a menopausal patient experienced from cortisone alone [25, 26] Potassium or nitrogen deficits, if they occur, can usually be controlled by the oral administration of potassium chloride and by special diets Testosterone eliminated the nitrogen deficit in one case The best guarantee against side effects now is to use, possibly intermittently, the smallest effective antirheumatic daily and total doses.

At this stage of our limited knowledge one should be content to control rheumatic symptoms without necessarily trying to reduce sedimentation rates completely to normal When the doses required to suppress completely rheumatic symptoms produce significant side effects, the daily (or triweekly) maintenance doses should be reduced or the plan of administration adjusted so that it will provide the maximal antirheumatic response with no or minimal side effects.

WITHDRAWAL OF CORTISONE OR ACTH

Clinical Pattern When the use of either hormone was discontinued, evidence of rheumatic activity usually returned rather quickly In about three-fourths of our cases the relapses were fairly complete within two weeks, but a continuing measure of relief accrued in a fourth of our cases In some of these cases most, if not all, of the relief was retained for from several

weeks to fourteen months before the disease relapsed. One of these patients has retained most of his relief five months after use of ACTH was stopped. Another had a short moderate relapse after withdrawal of cortisone and then a secondary remission which lasted eleven months Another patient maintained practically all her relief for fourteen months.

Whether or to what extent the prolonged relief after withdrawal of the hormone in these several cases was related to the previous use of the hormones, or was spontaneous, remains for further experience to determine

Withdrawal Phenomena. The discontinuance of use of these hormones was followed by the return of articular and constitutional features of the disease A curious posthormonal muscular weakness and exhaustion often came on two or three weeks after the sudden withdrawal of the hormones, it usually lasted three or four weeks, occasionally longer, and then disappeared. *It may have represented transient hypocortisonism. According* to certain investigators this phenomenon has not resulted when the courses of hormonal administration were tapered off by decreasing doses, rather than ended by sudden withdrawal

EFFECTS OF RELATED COMPOUNDS AND OTHER STEROIDS ON RHEUMATOID ARTHRITIS

We have tested for antirheumatic activity four adrenal cortex extracts and twelve steroid compounds more or less closely related chemically to cortisone.[41] Only two (both much more scarce than cortisone or ACTH) demonstrated significant antirheumatic properties *

A total of 900 mg. of free compound F was given intramuscularly within twelve days to one patient (Fig 12) and 700 mg. of compound F acetate within ten days to another. These preparations were active but somewhat less effective than cortisone A specially prepared and highly concentrated adrenal cortex extract (Upjohn), administered orally, gave one patient as *much relief as cortisone had Presumably its potency was derived* entirely or chiefly from its contents of compounds E and F.

Essentially negative results have accompanied the use of the following steroids, some of which are identical with cortisone except for one or two configurations [41] 11-dehydrocorticosterone (compound A of Kendall), 11-desoxycortisone (substance S [illegible] ace-
tate (DCA or DOCA), pregne [illegible]
hydroxy-11-keto-progesterone), [illegible]
droxy-progesterone; dihydro-cortisone acetate, 6-dehydro-cortisone acetate, Δ^5-pregnenolone and 21-acetoxy pregnenolone (artisone).

Desoxycorticosterone acetate (DCA) and vitamin C, given by Bilka and three of us after the manner of Lewin and Wassén, occasionally *resulted* in transient subjective improvement, in most cases results were entirely negative, articular swellings and sedimentation rates were not affected [42, 43]

USE OF CORTISONE AND ACTH IN OTHER CONDITIONS

[illegible] ACTH to
[illegible] he acute
pa [illegible]
ma [illegible] ese hor-
mones.[24, 44–46] Fever, acute polyarthritis, tachycardia and electrocardio-

* For these two preparations we are indebted to Drs E Gifford Upjohn and H F Hailman, The Upjohn Company.

graphic abnormalities usually disappeared within a few days Sedimentation rates and hyperglobulinemia were reduced (Fig. 13) Occasionally when the hormones were not given long enough, short, mild rheumatic recurrences developed but disappeared when the hormones were given again and did not recur. On reexamination of the hearts of the patients several months after use of the hormones was stopped, no definite evidence of new or increased old rheumatic carditis was found[15] It will take much more time to determine whether cortisone or ACTH will prevent the initial development or aggravation of rheumatic carditis

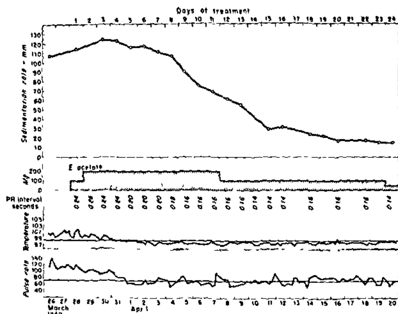


Fig 13 Effect of cortisone acetate (compound E acetate) on the sedimentation rate, P-R interval, temperature and pulse rate of a patient who had acute rheumatic fever

In several cases of lupus erythematosus disseminatus use of cortisone or ACTH was accompanied by disappearance of fever, arthritis, skin reactions, pericarditis, pleurisy and leukopenia Renal lesions appeared to be unaffected, albuminuria persisted Sometimes severe cardiac lesions have been unresponsive. Blood pressure increased sometimes Use of these hormones in lupus erythematosus disseminatus appears to be helpful often, perhaps even lifesaving, in acute crises Temporary remissions, not cures, were induced

In psoriatic arthritis the arthritis has been found to be more responsive to cortisone or ACTH than the associated psoriasis which, however, disappeared entirely when fairly large doses were given[17] In tuberculous arthritis (two cases) articular symptoms and signs and sedimentation rates decreased notably but results of articular biopsy, guinea pig tests and cultures remained positive for tuberculosis[25] Few cases of osteoarthritis have been studied by us or others One of our patients who had leukemia and incidentally primary osteoarthritis obtained articular relief from cortisone[23]

The articular symptoms and sometimes the intestinal symptoms of chronic ulcerative colitis have been responsive to these hormones in some cases.[25, 48]

It was not surprising to us to observe that the hay fever of two of our rheumatoid patients gave little or no trouble during the use of cortisone Neurodermatitis disappeared in one case and symptoms of bronchiectasis were markedly reduced in another.[25] The suppressive effects of cortisone on hay fever and asthma have been studied further at the Mayo Clinic *

STUDIES BY OTHER GROUPS

Independent investigations on the effect of ACTH on quiescent gout and acute gouty arthritis have been carried out by Wolfson and his associates,[49–51] by Robinson and his associates[52, 53] and by Hellman.[54] A close relationship was demonstrated between gouty arthritis and the function of the adrenal cortex. Various factors which may provoke acute gouty arthritis may do so by affecting pituitary-adrenocortical activity. ACTH provoked attacks of acute gouty arthritis in patients with quiescent gout but also promptly relieved patients with acute gouty arthritis Rapid amelioration of acute gouty arthritis has been reported by others.[37, 55, 56]

Confirmatory observations on the effects of cortisone and ACTH on rheumatoid arthritis, rheumatic fever, lupus erythematosus disseminatus, psoriatic arthritis, and other conditions have been made by a number of investigators [35, 36, 43 56–73]

COMMENT

Mode of Action The idea presented itself that rheumatoid patients might have an actual deficiency of production of endogenous cortisone Two observations prevented ready acceptance of this idea: (*a*) rheumatoid arthritis is not a feature or complication of Addison's disease—indeed rheu- ... (*b*) the doses of ... *much greater* than ... re, we concluded that if a deficiency of cortisone was present in rheumatoid arthritis or acute rheumatic fever, it was a relative, not an absolute, deficiency, perhaps one concerned with an increased destruction of cortisone or an increased tissue requirement for cortisone rather than a decreased production This supposition has been shared by Thorn and his colleagues[36] who have showed that the adrenals of most rheumatoid patients are responsive to a test dose of ACTH as indicated by the development of eosinopenia [37]

How does pregnancy relieve rheumatoid arthritis? Does it do it by an increased production of cortisone or cortisone-like steroid? How does jaundice produce its ameliorating effects? Does it do it by lessening the inactivation or destruction of cortisone or by improving the utilization of cortisone at the tissue level? Careful studies of pituitary-adrenocortical function during pregnancy, jaundice and chrysotherapy should be made

The fact that the effects of cortisone and ACTH are group-specific and demonstrable in a number of loosely related conditions suggests that the hormones act at the tissue level in some as yet unknown manner. The antirheumatic action of these hormones is not seemingly dependent on any of

* Carryer, H M, Koelsche, G A, Prickman, L E, Maytum, C K, Lake, C F., and Williams, H L. J Allergy, *21* 282, 1950

the metabolic or biochemical effects so far demonstrated Apparently cortisone restores (temporarily at least) to the tissues affected in these various diseases their defenses against the unknown primary irritating "causative agents." Further discussion of such working hypotheses is not warranted at this time.

Optimal Dosage and Method of Administration Further experience is needed to determine the optimal dosage and method of administration. In most of the conditions studied by us, best results have been obtained by the use for two to three weeks or more of fairly large doses of cortisone or ACTH until the maximal initial effects have been obtained, and then by the use of smaller daily doses. Thus in severe or moderately severe cases of rheumatoid arthritis or rheumatic fever the daily doses might be 300 mg. of cortisone or 75 to 100 mg of ACTH (Armour LA1A standard) for the first day, then 100 mg of cortisone or about 50 mg of ACTH daily for

days before the smaller doses are used. Mild rheumatoid arthritis has been found to respond to 50 mg of cortisone daily[59]

Several methods of administration of these hormones to patients who have rheumatoid arthritis are now being tested. These are (*a*) a short course of one or the other hormone (for about two to four weeks), withdrawal of

of small doses of both hormones, and (*d*) more or less continuous administration of either hormone

Since several of our rheumatoid patients, given courses of either hormone, obtained significant relief for several weeks or months after the use of the hormone was discontinued, the interrupted course method at present appears to us to be more practical, less wasteful of the scarce, expensive hormones and less productive of side effects than the continued use even of maintenance doses Because of our present limited knowledge, it would appear proper that every patient should be given the chance of demonstrating whether or not he can respond to a short course by a delayed relapse or prolonged remission If after two or three preliminary short in-

somewhere along the line to determine whether the patient has developed meanwhile the ability to maintain significant improvement without the hormones

Withdrawal of Hormone Three plans of withdrawal are being investi-

develop. A theoretic advantage is that in consequence of sudden withdrawal of exogenous hormone the adrenal glands may be induced to adjust more quickly and after successive courses may respond more efficiently to

sudden needs By use of tapered doses of cortisone or ACTH the adrenal cortex is given warning that it will soon be "on its own" By use of ACTH for a few days at the end of a course of cortisone, the adrenal cortex, inhibited by the preceding use of exogenous cortisone, may be aroused to increased activity by a few doses of ACTH.

CONCLUSIONS

The potential reversibility of rheumatoid arthritis has been further demonstrated. Our earlier presumption that cortisone and ACTH would prove to be useful against other articular or rheumatic diseases and also against those allergic conditions which are usually relieved by jaundice or pregnancy has been borne out. Before the use of these hormones can be regarded as a safe practical method of therapy, the optimal dosage and method of administration remain to be established so that the maximal antirheumatic effects can be obtained with minimal side effects. Some limited success in the prevention and control of side effects has already been attained A keynote for the investigation of the optimal use of these hormones is that we must learn how to cooperate with, rather than dominate or supplant, the functions of the pituitary-adrenal mechanism

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DISCUSSION

EDWARD C KENDALL

In 1930 a chemical and physiologic investigation of the adrenal cortex was undertaken in the biochemical laboratories of the Mayo Foundation for Medical Education and Research. In 1934 the first crystalline compounds were separated. These were designated "compounds A, B, C and D" In the following year two other crystalline compounds, E and F, were isolated, and definite chemical formulas were assigned to these compounds in 1937 and [illegible]

[illegible]

ments on mice and rats

In 1940 it became evident that the most important aspect of the investigation of the adrenal cortex was to make available sufficient amounts of the four compounds A, B, E and F to permit a detailed investigation of the value of these hormones in clinical medicine To this end attempts were begun in 1940 to prepare these compounds from a starting material more abundant than adrenal glands *

PARTIAL SYNTHESIS OF VARIOUS ADRENOCORTICAL HORMONES

When the hormones are separated from the adrenal gland the process is simply a matter of separation of these compounds from the fat, protein, water and other glandular material. When, however, the hormones are prepared from any source other than the adrenal gland an entirely different procedure is necessary. This procedure is known as "partial synthesis," because it involves a change in chemical structure The most promising scheme was to convert one of the bile acids into the hormones of the adrenal cortex, but whether or not this was possible was by no means certain in 1940

COOPERATIVE STUDIES

Just before the beginning of American involvement in the war, in the fall of 1941, requests were made to the National Research Council by the medical departments of the Army and Navy for a large supply of the hormones of the adrenal cortex, since it was believed that they would be of value in the event of military operations Indeed, a great stimulus to work on the adrenal cortex arose from the rumor that the pilots of the German *Luftwaffe* were injected with extract of the adrenal cortex and that this allowed them to fly at ease at an altitude of 40,000 feet or more

In 1941 a survey by the National Research Council showed that twenty-two laboratories in the United States were engaged in work related to the laboratory preparation of the hormones of the adrenal cortex A series of conferences was held in Washington Information was exchanged, and attempts to make the hormones were carried out by several different schemes

* This work has been supported in part since 1941 by grants from the Research Corporation, New York City.

COMPOUND A

Two of the most sustained investigations were made in the laboratories of the Mayo Foundation and in the research laboratories of Merck & Co, Inc In 1944 in the laboratories of the Mayo Foundation a small amount of dehydrocorticosterone (compound A) was made, and in December, 1945, a large sample of compound A was prepared by Merck & Co., Inc., by the method which had been devised at the Mayo Foundation The compound was employed in investigation of Addison's disease and was found to be of no value in this respect.

CORTISONE (COMPOUND E)

Only one more possibility remained. that the hormone now known as cortisone might prove to possess clinical value Shortly after this, cortisone was prepared in the laboratory of Merck & Co, Inc., by Dr L. H. Sarett, but the yield was very small. In October, 1946, a conference was held in New York concerning the preparation of cortisone After full discussion, there remained one question to be decided Should Merck & Co, Inc, spend many thousands of dollars and make 5 gm of cortisone by Sarett's original method, or should this method of preparation be given up and more research be

the second plan was adopted During 1947 several important contributions were made from both the laboratories of the Mayo Foundation and those of Merck & Co, Inc Dr Sarett devised an essential step to introduce the hydroxyl group at C_{17} and work carried out in the Mayo Foundation produced new methods for two other steps A much improved process for the manufacture of cortisone was ready by May, 1948, and since that time the material has been produced in ever-increasing amounts

To search for new chemical reactions which can be applied to the preparation of a substance such as cortisone requires test tubes, flasks and laboratory procedures carried out on a small scale To enlarge these operations to a scale which allows the use of several hundred pounds of starting material requires a different type of research, and the accumulation of information briefly described as "know how" To make cortisone available in adequate amounts has required an enormous amount of effort, time and money on the

for cortisone would be adequate and now it appears certain that a starting material more abundant than bile must be found. It seems probable that total synthesis starting with a simple compound such as benzene or naphthalene (moth balls) will be the only satisfactory answer As it is today, the preparation of cortisone is the most complicated process in the pharmaceutical laboratory.

Technical Difficulties Hench and his associates have presented several charts and summaries of laboratory work Some factors in the evolution of cortisone, for clinical use, however, are not shown in the charts Perhaps the most important are the manner of administration and the preparation of the material for injection.

* See p 131

It was most fortunate that a large dose was chosen at the outset. We now know that 100 mg. per day is required, and in some cases 150 or 200 mg is needed to bring relief. Had we used 25 or 50 mg. the whole project might well have failed. In addition, the material was employed in the form of a suspension of crystals. Had the crystals been larger the absorption would have been delayed and the result would have been different.

An important event not shown in the charts is the occasion on which I prepared several bottles of cortisone suspended in solution of sodium chloride and then had the bottles autoclaved. I went to New York and Dr. Slocumb soon found that the preparations were toxic. Those were trying days, but this experience led to identification of a new product which was contained in the cortisone To find a method to purify cortisone without substantial loss, and yet to keep the clinicians supplied, was not a simple matter.

Finally, I shall mention some of the difficulties in preparation of the solutions for injection We wanted to reduce the coarse crystals to a very fine powder, and for this we first tried grinding them in a mortar. This was not at all satisfactory Steel ball bearings in a flask which was rotated were then tried. These steel balls did produce a fine powder, but the iron oxide which was formed during the process turned the whole mass to a chocolate brown Nickel plated steel balls and silver nickel balls were used, but they dissolved In the end, glass beads employed with a wetting agent which acted on the crystals and improved the grinding process were found to be entirely satisfactory. These were some of the problems that were encountered and had to be overcome before cortisone was available for use in clinical medicine

COMMENT

Jaundice, pregnancy and the adrenal cortex appear to influence rheumatoid arthritis. These clinical observations must rest in turn on physiologic processes which concern the liver, adrenocorticotropic hormone of the pituitary and the hormones of the adrenal cortex To determine the etiology and to devise a possible relief of this syndrome are problems which can be solved only by co-operative effort. Cortisone has come from the laboratory as a first step in this investigation and in the hands of the clinician it has produced promising results, but we all realize how far it may be to the end

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DISCUSSION

RICHARD H. FREYBERG

The true limit of value of this work of Dr. Hench and his collaborators is inestimable, but certainly it is the most important contribution yet made to rheumatology. The detailed report and the impressive cinema illustrations which accompanied its presentation leave no doubt regarding the results, yet the conservatism of the investigators made them desirous of confirmation from persons outside their hospitals and laboratories. To that end Drs. Boland, Rosenberg, Holbrook, Bauer and I were invited to the Mayo Clinic, where we saw most of the patients who had received cortisone and ACTH and examined all of the data One of the most remarkable aspects of this visit was that it was planned to extend for only four days. Within that time we examined two patients before they received cortisone and then were able to

nine patients and in all nine the clinical results are in complete accord with those reported by Hench and his coworkers There is, then, abundant confirmation of the clinical effect of cortisone in at least nine patients in addition to those the authors have reported upon, with observations in several different institutions

Two patients studied by my collaborators and me include one with classical rheumatoid arthritis who shows a response to cortisone such as has been shown in the cinema illustrations The other patient had uncomplicated, quite severe rheumatoid spondylitis with shoulder and hip involvement. He has now been receiving cortisone for only nine days The benefit is very significant and follows the pattern seen in the usual type of rheumatoid arthritis involving joints of the extremities In both patients the systemic improvement, the speed and the certainty of the effects should be emphasized

The clinical benefits are indeed encouraging but we should not misunderstand or underestimate the great value of this work in contributing new approaches to study the mechanisms of rheumatic diseases. New portals are now open and we at last have some targets to shoot at There is, of course, much yet to be done How the effects of these hormones are accomplished, and the parts played by various organs and tissues in the production of the disease and its reversal are questions that will pose many problems requiring much research

EDWARD W BOLAND

To date we have studied the effects of cortisone in two patients, one with very severe and the other with moderately severe, rheumatoid arthritis of the peripheral type In both we witnessed the phenomenon of rapid regression of the clinical and laboratory manifestations of the disease as Dr. Hench has described In both, prompt exacerbation of the process occurred when

istration, she became afebrile and remained afebrile during the period of administration Within twenty-four hours she walked on her own power and fed herself Within seven days she literally danced a jig for the edification of

counts increased by one million cells and her hemoglobin by 1.6 grams One observation not heretofore mentioned should be recorded Prior to the administration of cortisone the electrophoretic patterns of serum protein were abnormal, the most significant changes consisting of elevations in the alpha and beta globulin and particularly elevations in the mucoprotein M_1 fraction. Within five days after beginning cortisone, striking decreases in these fractions in the direction of normal were noted.

EDWARD F ROSENBERG

A few weeks ago I was also given a small amount of cortisone, and immediately prepared an experiment along the lines which Drs Hench, Kendall, Slocumb and Polley have demonstrated. We chose a patient in whom the disease was a classic example of rheumatoid arthritis of fulminating variety. He had lost 30 pounds in ten months Over a period of ten days, while the preliminary observations were made, he was given daily injections of cholesterol without any effect On the eleventh day cortisone was substituted for the cholesterol without his knowledge Within one hour extraordinary improvement in his subjective symptoms was obvious. Within eighteen hours this patient, who had previously been able to walk only with a painful shuffle, was able to run back and forth in the halls of our hospital

W PAUL HOLBROOK

two years' duration and with minimal joint destruction. The one with minimal joint destruction recovered symptomatically 100 per cent, the other one perhaps 85 per cent I think the importance of this development cannot be overestimated We have been trying for years to find out what happens to the amino acid metabolism between acute disease and remission Now the work of Dr Hench and his associates has opened the door wide for a study of the mechanisms that occur with remission.

WALTER BAUER

We too have given cortisone to two rheumatoid patients and can confirm most enthusiastically the results reported by those who have preceded me. I can assure you, gentlemen, this is no humbug Dr. Hench places in our hands an agent which produces a remission seemingly as complete as any that occur naturally in this mysterious disease In addition he has demonstrated that, following the discontinuance of this hormone for as short a time as a few days, symptoms begin to return, indicating that the

underlying disease mechanism is still in play Many of us had better try to determine whether even patients with natural remissions still have some as yet unmeasured evidence of the underlying disease mechanism

° ° °

THE EFFECTS OF ENDOCRINE SECRETIONS ON ARTICULAR TISSUES AND THEIR RELATION TO AGEING PROCESSES*

MARTIN SILBERBERG AND RUTH SILBERBERG

An analysis of the role of hormones in skeletal growth and ageing is beset with many difficulties. Little is known about either the nature of age changes in general or the mechanism by which hormones act on tissues Nevertheless, an attempt will be made to review and to integrate some of the available data and, if possible, to advance a working hypothesis for future studies.

NATURE OF AGEING CHANGES IN ARTICULAR TISSUES

The articular tissues may, with advancing age, undergo the following changes (*a*) Stimulation of growth In the cartilage, proliferation and hypertrophy, and in the synovialis, hyperplasia take place (*b*) Regressive changes The cartilaginous matrix shows hyalinization and asbestos formation, or swelling and vacuolation, the cartilage cells break down and become liquefied, the synovialis and the ligaments undergo swelling, mucoid or fibrinoid change (*c*) A combination of growth processes and regressive changes leading to a picture typical of osteoarthritis The cartilage ulcerates and the underlying bone is bared, elsewhere in the articular surface overgrowth and vascularization of cartilage and synovial tissue may occur and marginal outgrowth of cartilage and bone may result, cyst formation is sometimes seen in the epiphyseal marrow Graded transitions exist from simple nondeforming age changes to the severe deformities found in osteoarthritis Yet, osteoarthritis has to be considered not a simple age change but a pathologic state

Rates of Ageing Changes The processes of growth, ageing and senescence proceed at a similar rate in individuals of similar genetic constitution, and within the same individual the time curves of different tissues show similar patterns[1] In mice, a certain parallelism exists between the progress of skeletal ageing, the development of the sex organs and the occurrence of spontaneous breast cancers[2,3] Within the skeleton itself, there is a close relationship between the age changes in the epiphyseal growth zones and those in the joints In slowly ageing strains of mice, the articular lesions begin at a later date than in rapidly ageing strains Once these changes

* From the [illegible]

of the American Medical Association

have set in, however, they may become severe irrespective of the speed with which a strain ages In the pathogenesis of osteoarthritis, the significance of constitutional or heredofamilial factors has repeatedly been stressed.[4-7] Individual differences do exist, however. Occasionally an aged individual will show no or only minor articular changes, although it belongs to a rapidly ageing strain, on the other hand, Scheuermann's disease may be interpreted as due to premature ageing of the vertebral cartilage.[8, 9]

RELATION OF GROWTH AND REGRESSIVE CHANGES TO ACROMEGALY AND OTHER DISEASE STATES

The early predominance in human cartilage of regressive changes over processes of growth has led to the interpretation that degeneration of cartilage represents the first event leading to osteoarthritis.[10] The predominance of proliferative processes as seen in cases of acromegaly was



Fig 14 Section from vertebral cartilage of seventy-four-year-old man who died of pneumonia, the cartilage is quiescent (X100)

thought to be a specific response to hyperpituitarism.[11-13] However, little attention has been paid to the presence and possible significance of primary growth processes in the cartilage occurring even in aged patients dying without any evidence of acromegaly.

Figures 14 to 16 illustrate some changes in the vertebral cartilage of patients dying from various unrelated diseases In such cases one may find some proliferation of cartilage cells and, though more rarely, there may be seen cartilaginous plugs ("Knorpelplomben") and suggestions of endochondral ossification, changes that have been interpreted as typically acromegalic Figures 17 to 20 illustrate some articular changes in acromegaly [9]

Moreover in small animals, processes of growth, especially hypertrophy of cartilage, regularly precede visible degenerative changes in the joints

Figures 21 to 24 illustrate some spontaneous articular lesions in the knee joints of mice.

A comparison between the spontaneous articular lesions in animals and the acromegalic joint changes in man reveals a certain similarity of both,



Fig 15 Section from vertebral cartilage of forty-five-year-old man who died of cirrhosis of the liver The cartilage is hyperplastic, and there is recartilagination at the zone of ossification with a suggestion of columnar arrangement of cartilage cells, regressive change is absent (X100)



Fig 16 Section from vertebral cartilage of fifty-year-old man who died of carcinoma of the tonsil There is no evidence of acromegaly, on the right side of the photograph endochondral ossification is suggested by columns of cartilage cells, a large plug of degenerated cartilage ("Ossifikationslücke") appears at the left side of the picture (X100)

although the acromegalic changes are far more advanced and widespread Under both conditions, growth of cartilage is intensified, and early growth precedes visible regressive changes Furthermore, the early acromegalic

hyperplasia likewise sets in in the superficial articular layers. Figure 18 shows this hyperplasia near the articular surface and the gradual formation of cartilage cell columns. In the deeper layers, the cartilage cells un-



Fig 17 Section from toe of aged acromegalic woman (Erdheim's case I). There is hyperplasia and hypertrophy of cartilage starting in the upper layers and leading to formation of short cartilage cell rows In the deeper layers the proliferating cells undergo hypertrophy so that the cartilage cell rows appear larger (X100)

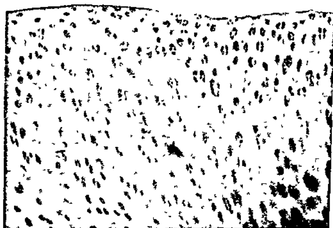


Fig 18 Section from tibia of middle-aged acromegalic woman (Erdheim's case II) [illegible]
become hypertrophic (X50)

dergo hypertrophy, a condition comparable to that taking place during epiphyseal growth The cellularity in the deeper layers of the cartilage in acromegaly may then be interpreted as due to crowding. [illegible] ertrophic

cells. These crowded cells, which do not ossify at a commensurate rate and

involve the deeper layers of the cartilage less often and to a lesser extent



Fig 19 Section showing vertebral increment same case as Figure 18 There is pronounced columnar arrangement of the cartilage, endochondral ossification is in progress (X110)



Fig 20 Section from head of femur, same case as Figure 18 There is ulceration and vascularization of cartilage, and marginal overgrowth and eburnation of underlying bone, the condition is indistinguishable from osteoarthritis (X25)

FACTORS AFFECTING SKELETAL AGEING

Skeletal ageing, although partly genetically determined, does not pro-

but more severely than females These sex differences in mice agree with observations in other species, including man, and point to some role of endocrines in the progress of articular ageing.[2, 3]

Nutrition Nutritional factors may profoundly alter the course of the articular changes [14] In rats, undernourishment retards the development

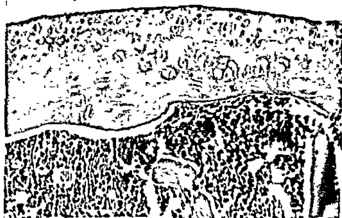


Fig 21 Section from upper end of tibia of seventeen-month-old male mouse The cartilage is slightly hyperplastic, there are no regressive changes (X200)



Fig 22 Section from upper end of tibia of twenty-month-old male mouse The cartilage is hyperplastic and hypertrophic, with early regressive change ("Verdaemmerungshoefe")

of age changes and of osteoarthritic lesions. In a majority of senile rats 750 to 1150 days old and underfed through life, the articular changes were slight or insignificant [15] On the other hand, in mice reared on a high fat diet, epiphyseal growth and development were accelerated far beyond ... early age, even

...tration of crude

acid extracts of bovine anterior hypophysis, Antuitrin G, or transplants of anterior hypophysis call forth changes varying from slight hyperplasia and hypertrophy to
changes to dest
synovialis and ligaments (Figs 20 to 25)



Fig 23 Section from upper end of tibia of twenty-one-month-old male mouse The cartilage is hypertrophic and hyperplastic, and there is regressive change and beginning vascularization (X200)

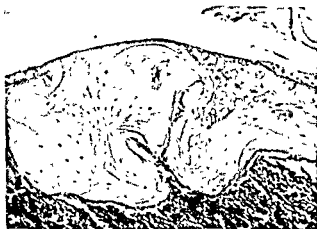


Fig 24 Section from upper end of tibia of twenty-four-month-old male mouse The cartilage is ulcerated, and there is eburnation of underlying bone (X200)

The severity of the lesions depends, among other conditions, on the species used, the form in which the hormone is administered, the duration of the treatment and the age of the animal at the beginning of the experiment As a rule, the younger the animal the more marked is the stimulation of growth processes, whereas with advancing age there is an accentuation of regressive changes Human cartilage seems to respond to hormonal

stimulation in a similar way In Erdheim's aged acromegalic patient (Fig. 17), growth of cartilage is less stimulated than in the middle-aged person (Fig 18) The cartilaginous increment of the intervertebral disks was found by Erdheim only in the younger of his two cases.

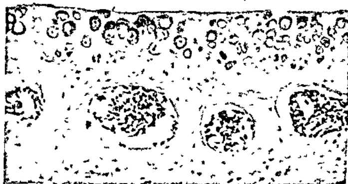


Fig 25 Section from epiphysis of four-month-old male mouse which had been fed from weaning on a diet containing 30 per cent fat The cartilage is hyperplastic and markedly hypertrophic and there is beginning degeneration ("Verdaemmerungshoefe") (X200)



Removal of the sex glands results in early proliferative processes (Fig 29) similar to those seen after administration of anterior hypophyseal hormones, and in combination with anterior hypophyseal hormone is particularly effective in producing severe articular lesions. Conversely, administration of thyroid, estrogenic and androgenic hormones leads to a condensation of cartilage and bone These hormones thus tend to counteract the articular changes elicited by anterior hypophyseal hormone[2, 3] (Fig. 30).

In human pathology,[5-7] the aggravation of joint lesions in hypothyroid-

ism and during and after the menopause is well known and suggests the presence of conditions comparable to those found in laboratory animals.



Fig 27 Section of cartilage from twelve-month old male mouse which had been castrated at the age of three weeks and had borne syngenesiotransplants of four anterior hypophyses and two ovaries from the age of four weeks. There is osteoarthritis advanced hyperplasia and hypertrophy, degeneration of cartilage and cartilagination of ligament (X60)

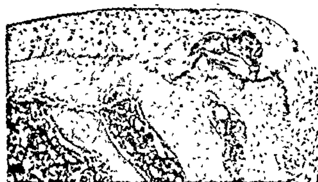


Fig 28 Section from head of femur of ten-month-old female guinea pig which had been injected daily with 4 cc of acid extract of bovine anterior hypophysis for sixty days The cartilage is hyperplastic, and there is a focus of necrosis in the deeper layers (X100)

PRIMARY GROWTH PROCESSES AS FORERUNNERS OF DEGENERATIVE LESIONS

The lesions observed in animals and discussed above may then be classified into spontaneous changes, largely or at least partly genetically determined as to incidence and severity, and into experimentally induced changes seen in particular after administration of anterior hypophyseal hormone

or subsequent to the removal of the sex glands. In earlier investigations,[17] the lesions produced by anterior hypophyseal hormone were thought to be specific, especially in view of their resemblance to joint changes found in cases of acromegaly. It seemed more likely that the experimental lesions represented an exaggeration of the spontaneous changes, particularly since



Fig 29 Section from upper end of tibia of five-month-old guinea pig which had been ovariectomized at the age of four months The cartilage is hyperplastic and somewhat hypertrophic (X100)



Fig 30 Section from upper end of tibia of eight-month-old female guinea pig which had received combined treatment with anterior hypophyseal extract and thyroid hormone for seven months The cartilage is slightly hyperplastic and hypertrophic, there are no degenerative changes (X100)

they appeared earlier, developed more rapidly and were more frequent than the latter.[2, 3] Similar difficulties may be encountered in the study of human material The finding in nonacromegalic individuals of primary proliferative processes without (or with negligible) regressive changes in conjunction with the observations in animals raises the question, whether the articular

changes in acromegaly are specific or whether growth processes do no precede degenerative changes more frequently than is generally thought perhaps even regularly. Such primary growth processes may rapidly and completely be overshadowed by regressive changes, or may take place at such an early date that they may not even be considered as forerunners of degenerative lesions. Moreover, it would be desirable to show in human and animal material that the morphologic similarity goes hand in hand with corresponding biochemical and biophysical findings. For lack of systematic investigations no such correlation can be made at the present time.[18]

ENDOCRINE FACTORS IN THE ETIOLOGY OF SPONTANEOUS ARTICULAR LESIONS

Is the morphologic similarity of the spontaneous and the induced changes more than coincidental and are similar factors involved in the causation of both? In other words, do endocrine factors likewise play a role in the pathogenesis of spontaneous articular lesions? There occur during the life-span of practically every individual, animal or man, periods of predominance of certain hormones. In females the sexual cycle and pregnancy represent such periods. In both sexes the cessation of sexual activity produces a hormonal condition intensifying the effectiveness of the anterior hypophysis. During any such period of predominance of a certain hormone over another, the articular tissues may react as they would under comparable experimental conditions, though less conspicuously. A summation of such minor stimuli may, in the end, cooperate in the induction of joint lesions.

Are the findings in animals applicable to human pathology? Although in various species the histologic structure of the joints varies as to detail, the basic constituents are the same in both man and animal. Variations in the thickness of the articular cartilage, which constitute a major species difference, may account for variations in the reactivity of the cartilage. Nutrients as well as injurious substances carried by the synovial fluid may reach all the cells of the thin articular surface of a mouse more readily than they reach the intermediate or deeper cells of the multilayered surface of a human joint. Moreover, mechanical stresses active in a joint of a quadruped[19] are different from those active in the corresponding joint of an erect-walking individual, a circumstance which may account for differences in the sites of predilection of lesions in animals and man, respectively.

Notwithstanding these differences, the same general principles seem to govern certain physiologic and pathologic phenomena in the joints of the various species. This applies also to the response to endocrine stimulation. That human cartilage is capable of reacting to anterior hypophyseal hormone has been demonstrated in cases of acromegaly. An analysis of these lesions is complicated by the simultaneous involvement of other endocrine glands which may in turn affect the articular tissues. Still, excessive amounts of hypophyseal hormone are produced in acromegaly, and the action of this hormone is probably not different from that of the hormone produced physiologically. One may thus assume that physiologic amounts of hypophyseal hormone may likewise affect the articul... ues and th

there is but a quantitative difference between the physiologic state and that in acromegaly In view of the results of step-by-step investigations in normal and experimental animals, [illegible] be interpreted as an extreme resp[illegible] lation. Simple age changes on the [illegible] form of a reaction, with lesions developing in the menopause or in hypothyroidism taking an intermediate position

Possible Mechanism of the Effect of Endocrine Secretions on Articular Changes How, then, do hormones affect the joint? Hypophyseal hormone acts in the absence of the thyroid and sex glands, and in mice syngenesiotransplants of anterior hypophysis are more effective than various extracts of the anterior hypophysis [2, 3] We do not know which one or how many of the anterior hypophyseal hormones may be involved in these reactions nor do we understand their mode of action However, some explanation based on analogy may be offered· The growth-maintaining hormone of the anterior hypophysis increases both water content and nitrogen retention in various soft tissues [20] A similar effect exerted on the articular tissues might promote both growth processes and premature degeneration of the cartilage These changes may render the articular tissues more vulnerable to the action of other and especially of mechanical factors

The question may be raised whether it is permissible to speak of an age-promoting effect notwithstanding the presence of apparently increased growth processes in the joints The answer should be in the affirmative inasmuch as one has to deal with tissues of limited growth capacity which declines with advancing age Anterior hypophyseal hormone seems to elicit from the cartilage a maximum growth response, only to exhaust its growth capacity prematurely and thus to induce premature ageing [2, 3]

In contrast to the effect of anterior hypophyseal hormone, the evidence, both positive and negative, points to a condensing effect of thyroid, estrogenic and androgenic hormones on the cartilage [2, 3] An equilibrium between anterior hypophyseal hormone and thyroid, estrogenic and androgenic hormones may aid in maintaining the physiologic state of the articular tissues Disturbances of this hormonal equilibrium as well as metabolic disturbances of nonendocrine nature may cause changes in the composition of these tissues with all their sequelae

In conclusion, what is the relative significance of hormonal factors in the causation of osteoarthritis? Osteoarthritis, like many other diseases, is the result of the interaction of certain stimulating factors and the substratum on which they act

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DISCUSSION

JOSEPH W JAILER

It is well to emphasize, although Drs Martin and Ruth Silberberg have mentioned it, that hormones do not initiate physiologic and biochemical processes but accelerate or inhibit the rate of the reaction Many examples of this generalization can be cited

It has been known since 1922 as a result of the work of Long and Evans and Stockard, that the pituitary gland accelerated linear growth in animals Stockard went on to demonstrate that the chronic administration of a crude growth hormone preparation caused the equivalent of acromegaly in dogs and ascribed differences in appearance of various strains of dogs to differences in functional activity of the pituitary

of the thyroid
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effect on the uterus vagina and mammary gland only and that the androgens exerted their effects on the secondary sex characteristics of the male Further

matrix of bone The estrogens have a marked effect on electrolyte metabolism and may also affect bone similarly

Gradually a new concept of bone formation has come into existence It appears entirely possible that the growth hormone is concerned with the deposition of bone at the epiphyses and that with the onset of puberty the sex steroids come into play They also facilitate growth of bone but, in addition, cause a maturation of the skeleton and perhaps a closing of the epiphyses

It is not known if the growth hormone of the pituitary ceases to be secreted at puberty In fact, there is some evidence that it is secreted throughout life Now, it is entirely possible that at the menopause for example, when the

pituitary is released from its inhibition by the sex steroids, there is an oversecretion of growth hormone. In the presence of normal wear and tear that comes with age, together with nutritional factors and trauma, *it is possible that* the growth hormone has a suitable substrate upon which to act, and proliferative and hyperplastic changes might ensue. The working hypothesis presented is very logical. However, substitution therapy with either estrogens or androgens is not the therapeutic answer because it is not easy to inhibit the pituitary in such a simple fashion

The carrying over of data obtained in rodents to the human being is fraught with danger The bone structure in the rodent is different, for example, the epiphyses in the rat never close, so that growth is possible even in the adult. It is for that reason that acromegaly cannot be obtained in the rat

* * *

ABSTRACTS

STUDIES ON THE POSSIBLE RELATIONSHIP OF PITUITARY-ADRENAL FUNCTION TO ARTHRITIS

GEORGE W THORN, PETER H FORSHAM, JOSEPH E WARREN
AND THEODORE B BAYLES

Pituitary adrenocorticotrophic hormone (ACTH, Armour) in normal subjects and in patients with intact adrenals stimulates the secretion of electrolyte-regulating, carbohydrate-regulating and androgenic adrenal steroids A fall in the level of circulating eosinophils (direct determination) and an increase in the urinary excretion of uric acid represent sensitive indicators of the increased secretion of 11-oxy-adrenal steroids Using the eosinophil change as a reflection of adrenal cortical function, reactions to the administration of pituitary ACTH have been investigated in patients with rheumatoid arthritis, rheumatic fever and gout. The initial eosinophil level provides a simple measure of adrenal cortical activity in selected instances The response to ACTH is a semiquantitative method of estimating the reserve capacity of the gland.

Adrenal steroids may modify the course of an infection Of particular interest is the fact that the pituitary-adrenal system serves as a link between the effects of psychologic and emotional factors and measurable changes in metabolic processes

DISCUSSION*

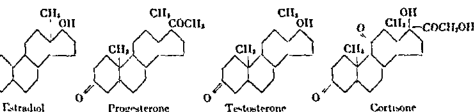
It has pleased me to hear defended, in the papers by Drs Thorn and Hench and their associates, a thesis which I have always held namely, the origin of rheumatism in endocrine glands

Although rheumatism appears under different aspects, I believe that several types of rheumatism are closely related and that the disease is "one and indivisible" Rheumatism has its origin not in outside causes but in the circumstances inherent in each case, in agreement with the views proclaimed long ago by our famous colleague, Dr Pidoux "La maladie est de nous, en nous, par nous" I also believe that rheumatism and gout are not entirely unconnected.

In various cases of rheumatoid arthritis my associates and I, by using sex hor-

* By Mathieu-Pierre Weil.

mones, have obtained results which are often interesting, sometimes remarkable, and in certain cases really extraordinary. These products—estradiol, progesterone and testosterone—are chemically quite comparable to cortisone, as will be seen from the following diagrams



In menopausal rheumatism, results remain almost constant. In generalized inflammatory rheumatism, the real rheumatoid arthritis, results are not as satisfactory, however, in certain cases they render more effective the employment of other remedies such as gold therapy, making the results more rapid and complete Complete cures are quite exceptional but they have occurred. In contrast to the results obtained with cortisone or ACTH, our results are more definitive

Although the patients we have treated were suffering from local inflammation and edema that characterize rheumatoid arthritis, they were more or less advanced in age and roentgenograms showed diffuse osteoporosis We now wonder if this postmenopausal or presenile osteoporosis, far from being the effect, is not perhaps the cause of this particular painful condition The cases, however, had every appearance of rheumatoid arthritis

One may ask oneself if our results with implantation of hormones, and the results obtained with pituitary and suprarenal extracts, have not an identical physiopathologic basis

Certainly we have not reached the goal, but we are approaching it The observations of Hench and Thorn and their coworkers are full of promise and allow us to hope that this goal may perhaps be reached in the near future

THE EFFECT OF Δ5-PREGNENOLONE ON URINARY 17-KETOSTEROID EXCRETION AND SYMPTOMATOLOGY OF ANKYLOSING SPONDYLARTHRITIS, WITH A NOTE ON THE RESULTS OF FRACTIONATION

ROLAND A DAVISON AND PETER KOETS

Increased urinary excretion of 17-ketosteroids has been demonstrated in ankylosing spondylarthritis (Marie-Strumpell disease). It is observed in both male and female patients and is present in early cases with little demonstrable joint change, as well as in those patients who have had the disease for many years and who show the typical findings of the advanced case

Δ5-Pregnenolone is a steroid having several actions not characteristic of other steroids Its chemical composition makes it a logical process material to act as a precursor of many active steroids When normal individuals are subjected to acute stress and fatigue, adrenal cortical activity is accelerated and increased rates of 17-ketosteroid excretion are observed Pregnenolone administered under such conditions lowers the 17-ketosteroid excretion, improves performance and combats fatigue. This steroid has not to our knowledge been used in disease states. Its general properties, its freedom from toxicity, and its ability to lower urinary 17-

appears that the cells freely absorb the gold, however, the presence of gold on, in, or within the cell membrane cannot be differentiated

The distribution of gold in the blood elements in relation to time was then investigated. Under Nembutal anesthesia the saphenous vein of a rabbit was cannulized, the plastic tube being inserted up to the iliac bifurcation Radioactive gold sodium thiosulfate was then injected intravenously and aliquots of blood were removed at various intervals. Each aliquot was

Table 25 In Vitro Association of Gold with Erythrocytes

MILLILITERS OF GOLD SOLUTION ADDED	ERYTHROCYTES*	SUPERNATANT*
0.1	1000	3500
0.2	1600	7200
0.3	2000	10500
0.4	2600	15200

* Data expressed as counts per milliliter per minute.

separated into the following portions. whole blood, erythrocytes, plasma, and white blood cells. Hematocrit measurements were taken with each sample and the cellular components were accurately measured for volume by packing under centrifugation Table 26 contains the data from such an experiment The heading "plasma component" *refers to the value obtained* when the hematocrit value for plasma is used to interpolate the number of counts in whole blood contributed by plasma, and serves as a check on the experiment.

Table 26. Gold Partition in Blood

HOURS	WHOLE BLOOD*	PLASMA*	R B C*	W B C*	PLASMA COMPONENT*
1	lost	24,420	710	510	16,115
2	10,280	20,270	570	2,760	13,600
3	8,600	13,300	285	2,500	9,600
4	8,420	14,130	396	2,840	10,200
5	4,230	6,080	518	1,070	4,380

* Values represent corrected counts per milliliter per minute.

It can be seen from these data that by far the greatest amount of gold lies in the plasma The white blood cells are seen to be relatively high in gold content, however it must be pointed out that this is the value for 1 cc of cells, and that actually they contribute very little to the total content of whole blood

The Removal of Gold from the Blood In the course of several of our experiments it was noticed that the rate at which gold was removed from *the blood stream was inconstant, and not directly related to the time elapsed*

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sembled one another greatly. Gold was found to leave the blood stream at

a regular rate and then, at from two to five hours, depending on the animal, its concentration increased and then again fell off at a uniform rate. Samples were taken at thirty-minute intervals except in one rabbit, from which one-,

a uniform rate (Fig 31).

This same type of curve is suggested in human beings, although it is not as definite. In a healthy young male the upswing was found to occur in

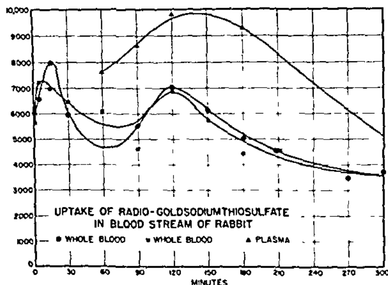


Fig. 31

from two to four hours, in a middle-aged female arthritic subject, it was from three to five hours

The Nature of Gold in the Blood Little is known of the form gold salts assume once they are introduced into the blood stream and we desired to know whether they remained as the administered material or became altered For this purpose blood was withdrawn from rabbits forty-eight hours after receiving radioactive gold sodium thiosulfate. This was heparinized and centrifuged Samples of the plasma were then taken and the remainder put into cellophane bags which were immersed in physiologic saline solution After forty-eight hours with constant stirring, the radioactivity inside and outside the bags was tested after acid digestion and electrolytic recovery of the gold It was found that essentially no gold had dialyzed and that the total original activity had remained inside the membrane This experiment has been repeated many times with the same result Controls using the same radioactive gold salt solution proved to be freely dialyzable

The rate at which this association took place was of interest so dialysis

experiments were set up with blood plasma samples drawn at intervals of five minutes to five hours after administration. It was found that the combining of the gold salt and the blood protein took place within five minutes Table 27 shows the data from one such experiment.

Here plasma samples were measured to check the experiment and it can be seen that the values for these samples check closely with the sum of the activities inside and outside the membrane. It is presumed that the four-hour value in the "outside" column is erroneous, due to a leak in the cellophane membrane

This process will take place in vitro, but at a much slower rate It was found that at the end of five minutes 50 per cent of the radioactive gold sodium thiosulfate had combined with the plasma proteins; at thirty minutes, 61 per cent, and at one and one-half hours, 71 per cent had combined

In order to further check the association of this gold salt with the plasma proteins, precipitation with 10 per cent trichloracetic acid was carried out Blood was withdrawn by cardiac puncture from rabbits previously given

Table 27. Dialysis of Interval Plasma Samples

HOURS	PLASMA*	INSIDE*	OUTSIDE*	SUM*
1	22,780	15,730	130	15,860
2	18,125	16,210	51	16 260
3	15,090	14,060	110	14,170
4	15,170	12,440	2,050	14,490
24	6,335	5,532	94	5,625

* Data expressed as counts per minute per milliliter The sums of the inside and outside radioactivity counts have been rounded off to the nearest five units

the radioactive gold solution This was heparinized and the plasma was obtained Trichloracetic acid precipitation was carried out and samples of the precipitate, the supernatant liquid and the washings were taken It was found that about 10 per cent of the activity remained in the supernatant liquid, 1 per cent in the washings and the remainder in the protein precipitate. This would indicate that the combination is chemical in nature and possesses a rather strong bond

Radioactive gold sodium thiosulfate given to one normal male and to one male rheumatoid arthritic patient was shown to be nondialyzable after twenty-four hours.

Donor Experiments in the Normal and Jaundiced Rabbit Since gold sodium thiosulfate is altered when introduced into the blood stream, it was of interest to see if the distribution of this substance would vary from that of the salt when administered directly to the animal Rabbits were given the usual amount of radioactive gold sodium thiosulfate and forty-eight hours later were bled by cardiac puncture This blood was heparinized and the plasma was separated by centrifugation Twenty ml of this clear plasma was then given intravenously to a second rabbit, and in forty-eight hours, after perfusion with physiologic saline, this rabbit was sacrificed

The percentage of gold per gram of tissue was increased in most cases over that found when the radioactive gold salt was given directly Table 28 shows such data; one column contains values for the donor rabbit and the

second, for the recipient. The third column represents the factors by which the concentration of gold was increased or decreased

Similar experiments were carried out using jaundiced rabbits Under ether anesthesia the common bile ducts of rabbits were ligated. After seven to ten days, when the animals were markedly icteric, their blood was withdrawn by cardiac puncture and they were perfused with normal saline and

Table 28 Gold Distribution in the Normal Donor and Recipient Rabbit

TISSUE	DONOR*	RECIPIENT*	FACTOR*
Liver	25	.185	.7
Spleen	278	.21	75
Kidneys	522	.976	1 8
Gut	025	084	3 3
Tendon	05	.189	3 9
Synovialis	02	116	5 8
Muscle	014	058	4 8
Articular cortex	031	307	9 9
Skin	045	113	2 5
Plasma	152	186	1 2

* Data expressed as percentage of total gold injected per gram of tissue

sacrificed. From the blood, clear, icteric plasma was obtained This was then administered intravenously to a normal rabbit, samples of plasma being saved for assay The recipient rabbit was sacrificed after forty-eight hours, having been perfused with normal saline beforehand Samples of the tissues to be assayed were taken in duplicate from both animals Table 29 contains the data obtained from these experiments Each value is an average

Table 29 Gold Distribution in the Jaundiced Donor and Normal Recipient Rabbit

TISSUE	DONOR*	RECIPIENT*	FACTOR*
Liver	195	149	− 0 7
Spleen	372	362	− 0 9
Kidney	54	2 10	3 8
Gut	023	50	21 7
Tendon	024	15	6 2
Synovialis	025	29	4 9
Muscle	0061	044	7 2
Articular cortex	043	10	2 3
Blood	087	44	5 0
Serum	083	49	4 7
Plasma	103	166	2 0
Skin	05	16	3 2

* Data expressed as percentage of total gold injected per gram of tissue

of seven or eight samples The first column represents the jaundiced donor rabbit; the second, the normal recipient, the third represents the factor of increase or decrease in the two sets of samples

Placental Transmission of Gold In order to determine whether or not gold sodium thiosulfate could cross the placental barrier, the radioactive form of this salt was administered intraperitoneally to pregnant mice. After

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Placental Transmission of Gold In order to determine whether or not gold sodium thiosulfate could cross the placental barrier, the radioactive form of this salt was administered *intraperitoneally* to pregnant mice After

forty-eight hours, and in these cases just before term, the mice were sacrificed. Fetal and placental samples were taken for assay and found to contain 0 24 and 17 per cent of the total gold injected per gram, respectively. Radioautographs were made to show the distribution of gold in the fetus (Fig 32).



Fig 32 Radioautograph of mouse embryo at term

COMMENT

It can be seen from the presented data that by far the greatest amount of gold in the blood is present in the fluid fraction Serum is found to have, on the average, about 4 per cent less than plasma, which might represent the amount held by the fibrinogen fraction Contrary to previous reports,[3] the erythrocytes were found to contain gold in significant concentrations. This was true under both in vivo, and in vitro conditions, and in spite of repeated washings. Washing of the erythrocytes decreases the gold held by them, which might indicate mechanical dispersal of gold adsorbed in the cell membrane, or a loss due to equilibrium phenomena.

The chemical state of soluble inorganic gold salts in the blood stream is of interest, both academically and from therapeutic considerations. The binding power of the plasma has been demonstrated in the case of other metals Sturgenor, Koechlin and Strong[4] have shown that iron, copper, and zinc are bound by the beta globulin of the plasma Scott[5] has shown that silver also is mostly bound with the globulin fraction DeWitt[6] stated in 1918 that the gold in blood might be in the form of an albuminate, and recently Freyberg, Block, and Preston[3] expressed the opinion that gold was probably held by the plasma proteins, although no experimental evidence was stated

The mechanism by which gold becomes bound to the plasma proteins can only be speculated on It is possible that this takes place directly in the blood stream, although it has been pointed out that when gold is mixed with whole blood in vitro only 71 per cent of the gold becomes bound in one and one-half hours, while in vivo practically all of it is bound within five minutes It is possible that this could take place in the liver, however, in a severely jaundiced rabbit this conjugation can be shown to take place in just as short a time.

The uptake of gold from the blood stream, we thought, might also be connected with liver function The increase in blood gold concentration after an initial decrease could only be explained by postulating an early

removal and subsequent liberation of the substance It was thought most probable that the liver was responsible for this phenomenon In the hope of demonstrating this, samples of mouse livers were removed at intervals over a period of five hours after administration of gold However, this merely showed a gradual increase in the gold concentration, and not the curve inverse to that of the blood

If gold exerts its therapeutic effect by acting directly on the joint tis-

stance In general, clinical experience has shown that higher concentrations of gold are more effective in the treatment of rheumatoid arthritis, however, they are also more toxic It might be pointed out that apparently the concentration of this gold protein conjugate is not increased in the liver, which



Fig 33 Radioautograph of rat kidney, using gold^{198}

At the present time we are attempting to isolate the fraction or fractions of plasma which contain the majority of the gold In view of the evidence at hand, it would seem that a concentrated gold plasma-protein preparation might be advantageously studied further.

CONCLUSIONS

1 Gold is carried mainly in the plasma component of the blood.

2 Shortly after the introduction of gold sodium thiosulfate into the animal's blood stream, it is altered in such a way so that it will not dialyze through a cellophane membrane This alteration will also take place in vitro, but at a much slower rate

3 When this altered gold complex is administered to an animal intravenously, the distribution of gold in the tissues of the body is significantly altered, in general, the concentration is higher

4 Transmission of gold across the placental membrane has been demonstrated.

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FOLLOW-UP STUDY OF FOUR HUNDRED AND FIFTY-FIVE CASES OF RHEUMATOID ARTHRITIS TREATED WITH GOLD SALTS*

DAVID H. KLING, JOHN P. VENTO AND DAVID SASHIN

The investi[illegible] other therapy in
rheumatoid ar[illegible] s. (*a*) Is gold a
specific? (*b*) [illegible] "natural" course
of the disease and to a greater degree than other measures? (*c*) If so, is the
amelioration [illegible]

A definite [illegible] ble until the riddle of the etiology of rheumatoid arthritis is solved.

The second question is difficult because the knowledge of the "natural" course of the disease is limited Individual evaluations depend on the ma-
[illegible] atypical cases are included,
[illegible] he disease than if there is
[illegible] l *rheumatoid arthritis.*
[illegible] arthritis can be charted
at the present time, a conclusion of the effect of gold or any other therapy must be based on a well defined material The following factors which may influence the results favorably or adversely should be taken into consideration

1 Gold can affect solely the inflammatory phase of the disease; therefore only active cases should be included.

2. The series should contain only typical cases and exclude doubtful and atypical forms such as palindromic arthritis, post-traumatic, post-infectious arthritis, Marie-Strumpell disease, Still's disease or active rheumatic fever, which follow a different course

3 The series should be consecutive

4. Severity, duration of the disease, age and sex distribution should be thoroughly analyzed.

5 It is important to enumerate the gold compounds used, and single and total dosages. These vary greatly with different authors and influence the results as well as the incidence and severity of reactions

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The answer to the third question can only be given by a long-range follow-up study. However, the efficiency of a new therapy must be temporarily measured by immediate results. It makes a great difference if significant improvement is obtained within a period of three or six months, the average duration of a gold course, or is delayed for a number of years Reports of immediate results are further important for the speedy elimination of inefficient and harmful measures which have been highly publicized

In order to answer the second and third questions we studied the immediate and long-range results in 455 cases of typical, active rheumatoid arthritis of the peripheral joints in which the patients received one or more courses of gold therapy. A total of 755 courses were given. Eleven patients, including five with valvulitis, gave a history of old rheumatic fever, but the arthritis was chronic and progressive and did not yield to an adequate course of salicylate therapy Sixteen patients had psoriasis All others were typical.

CLINICAL MATERIAL

Of the cases studied, 27 5 per cent were males and 72 5 per cent were females. The ages varied from fifteen to eighty years, the average age being 44 8 years The duration of the disease ranged from three months to twenty-five years, the average duration of the arthritis prior to gold therapy was seven and one-half years. In only 11 2 per cent was the duration less than one year

The disease was mild in 3 7 per cent, moderate in 43 9 per cent and severe in 52 6 per cent In each case there was clinical, roentgenologic and laboratory evidence of a nonspecific inflammatory progressive arthritis, with various degrees of systemic involvement

The material was unselected and consecutive except when a contraindication was found or the patient declined gold therapy

PREPARATIONS AND DOSAGES

Gold sodium thiosulfate was [illegible] cent of the cases Solganal B was giv[illegible], and calcium aurothiomalate [illegible], Aurocein and Myochrysin, were give[illegible]. The standard dosage consisted of injections of 25 t[illegible] mg once or twice weekly up to a total dose of 1000 mg In some cases single doses of 100 mg and a total dose of 2500 mg were given Sixteen cases who received only 250 to 500 mg were included because the course was discontinued on account of toxic reactions

CLASSIFICATION OF RESULTS

The following classifications were adopted

1 Remission. Loss of all objective and subjective symptoms of inflammatory activity of the joints and a return of the sedimentation rate to normal

2 Great improvement. Low degree of activity and a variable amount of subjective symptoms with the sedimentation rate either normal or markedly lowered Only remission or great improvement was regarded as significant

3 Moderate or slight improvement Various degrees of objective and subjective amelioration and some decrease in the sedimentation rate.

4 Unimproved or worse

IMMEDIATE RESULTS

After the first course 13 per cent of the patients were in remission, and 38 4 per cent were greatly improved, thus, 51 4 per cent had a significant amelioration. There was moderate or slight objective improvement in 36 5 per cent, while 12 1 per cent were not improved or were worse (Table 30)

Statistical analysis showed that the duration of the disease, its severity, and the sex of the patient had only a slight influence on the results.

The subsequent courses did help to maintain the rate of significant improvement at about 50 per cent. However, our material does not show an *increase of significant* improvement after repetition of the first course

Sedimentation Rate The Westergren sedimentation rate read after one hour was found to give a more accurate index to the inflammatory activity than any of the numerous "corrected modifications"

Table 30 Results after the First Course

IMPROVEMENT	NUMBER OF CASES	PERCENTAGE
Remission	59	13 0
Great	175	38 4
Moderate	96	21 1
Slight	70	15 4
None or worse	55	12 1
Total	455	100 0

The average sedimentation rate before the first course was 48 5 mm After the first course it dropped to 25 7 mm Before treatment only 2 7 per cent *of the patients had a normal sedimentation rate, whereas 23 3 per cent* had a normal rate after treatment

The clinical course paralleled the sedimentation rate in about 90 per cent of the cases

Reactions Reactions after the first course occurred in 36 per cent of the cases treated. Of these, 61 4 per cent were mild, 37.7 per cent were moderate, and 6 7 per cent were severe All severe reactions involved the skin and no dangerous visceral reactions, blood dyscrasias, or neurologic complications were encountered No fatalities occurred which were related to gold therapy.

[illegible] analgesia, usually salicylates and codeine [illegible] nd exercises were recommended for home [illegible] atients received various physical therapy treatments at the office However, the end results were no better than in a group *of 175 cases which did not have such treatment.*

Orthopedic measures were used mainly in the prevention and correction of deformities.

Controls 1 Self control: With the exception of sixteen early cases with duration of less than three months, all others had received previous therapy of various types for months or years without significant *improvement* of any duration.

2 Two hundred and fifteen comparable patients who declined gold therapy or had contraindications to it were given various regimes which at one

time or another have been recommended. Some degree of objective improvement was noted in from 10 to 15 per cent. The relapse rate in these cases after several weeks to six months was about 60 per cent.

On the basis of our material, we answer the question whether gold compounds influence rheumatoid arthritis to a greater degree than other measures, in the affirmative, as far as the immediate results are concerned.

FOLLOW-UP

We now proceed to deal with the third question, namely, whether the amelioration is only temporary or of long duration, by an analysis of the follow-up.

Of the 455 cases which took one or more gold courses, 139 (31 per cent) were followed up for one year or less. The remaining 316 cases were followed up from more than one to as long as seventeen years. The percentage of cases followed up was 69.5 per cent in the second year, 79.7 per cent in the third year, 73.1 per cent after five years, and 57.7 per cent after ten years (Table 31).

Table 31. Follow-up

YEARS	MAXIMUM POSSIBLE FOLLOW-UP	NUMBER OF CASES FOLLOWED UP	PERCENTAGE FOLLOW-UP
6 mos. to 1 yr.	455	455	100
1 to 2	455	316	69.5
3	295	235	79.7
5	231	169	73.1
10	71	41	57.7

Table 32. Results at Last Examination

CONDITION	NUMBER OF CASES	PERCENTAGE
Remission	40	12.7
Great improvement	103	32.6
Moderate improvement	95	30.1
Slight improvement	52	16.4
Stationary or worse	26	8.2
Total	316	100.0

The following four methods of estimation were employed:

1. Results of the last examination of 316 cases followed up for over a year were tabulated (Table 32).

Of these cases, 45.3 per cent were in remission or had marked improvement, 46.5 per cent were moderately or slightly improved, and only 8 per cent were stationary or worse. This method may give too favorable an impression because of the possibly greater percentage of failures among those cases not completely followed up. Secondly, it does not reveal the condition of the patient during the long intervals between immediate results and

last check-up However, it is commonly used by other authors and is presented here for purposes of comparison with their results.

Because of the considerable loss in percentage of the cases followed up in successive years of the study, a separate estimation was made on 152 cases who received more than one gold course In these cases the follow-up fluctuated between 99 4 per cent in the second year and 91.8 per cent in the fifth year From six to ten years the follow-up amounted to 77 8 per cent The percentage of significantly improved cases differed only slightly from that of the whole group. The conclusion, therefore, of maintenance of the significant improvement in successive years is confirmed.

2 A breakdown year by year (Table 33) showed that the percentage of significant improvements reached a peak of 63 6 per cent after one year

Table 33 Percentage of Remissions and Great Improvement During Each Year of Observation

YEARS	CASES	PERCENTAGE
First	316	63 6
Third	235	54 7
Fifth	169	49 7
Ninth to tenth	54	46 3

and dropped to 46 3 per cent in the tenth year. It fluctuated in the intervening years between these values This represents a superiority of at least 30 per cent above the best results (15 per cent) in the control group treated by other means.

3 The follow-up status of the patients was compared with the results after the first course or the immediate results Of the group which was in remission after the first course, 80 per cent remained in remission or dropped only slightly to "great improvement" during a period of five years. Of the group which had great improvement after the first course only 56 per cent maintained great improvement or achieved remission during the five-year period The difference is statistically significant and permits the conclusion that cases which achieved remission during the first course had a better chance to remain significantly improved up to five years This probably also holds good for the period of six to ten years

Table 34 Relapses in Various Years of Follow-up in Cases Which Were in Remission or Greatly Improved

YEAR	NUMBER OF CASES	PER CENT OF RELAPSE	NO RELAPSES	AVERAGE YEARS IN RELAPSE
5	116	57 8	42 2	1 2
10	32	75	25	3 2

Of the patients who had only moderate, slight or no improvement in the first year, 20 per cent became significantly improved or in remission after two years It cannot be decided how much this is due to subsequent gold courses and how much to a "natural" abatement of the disease.

4 An analysis of the relapses should consider not only the number but the degree and the duration in order to evaluate the real loss of improvement through the years of follow-up (Table 34).

Out of 116 patients who were in remission or greatly improved after the first course, 42.2 per cent had no relapse whatsoever and 57.8 per cent had relapses at five years In the tenth year of follow-up, out of thirty-two such patients, 25 per cent experienced no relapses and 75 per cent suffered relapses. The above incidence of relapses occurred in patients who did not receive additional gold therapy, as well as in patients who had subsequent courses during the periods of follow-up The relapse rates estimated among those in whom gold therapy was suspended are still higher. They amount to 62 per cent after five years and 94 per cent for a ten-year follow-up period.

Analyzing the relapses, we note that only 7 per cent were total, whereas 93 per cent were partial relapses The average duration of the relapses amounted to about one year out of five years, and to 3.2 years out of ten of observation

The relapses were stationary for the whole period of observation in thirty-six patients out of the 190 who were in remission or greatly improved after the first course Thirty-three of these were partial and only three were total

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In a compilation of the results of chrysotherapy in approximately 6000 cases, about half of them published by American authors and the other half by foreign writers, the average of significant improvement is almost equal (51.2 per cent) to our results This also applied to the percentage of nonimprovement (11.7 per cent in the combined series and 12.1 per cent in our material) In a control series of 215 patients treated by other methods, some degree of objective improvement was achieved in only 10 to 15 per cent This superiority of chrysotherapy has also been demonstrated by Ellman, Fraser, Waine, Secher and their associates, using rigid controls and follow-up periods of observation.

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COMMENT

To draw a balance between the advantages and the shortcomings of gold therapy or any other therapy in rheumatoid arthritis is a formidable task. On the credit side this investigation has brought out the following.

1 Significant improvement was achieved after one gold course of three to six months duration in about 50 per cent of 455 cases of typical, active rheumatoid arthritis of the peripheral joints in adults. The disease was severe in over half of the patients and mild in only about 4 per cent With the exception of sixteen, these patients had previously been unsuccessfully treated, the majority for years, by different methods.

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Several authors (Snyder, Thompson, Waine, and their associates) and ourselves have given gold after prolonged failure of other therapy, with significant improvement in 30 to 60 per cent of cases

2 About half of the cases achieved significant improvement after the first course. This percentage was maintained with slight fluctuations for a period of ten years. The results are at least 30 per cent better than in the control group treated by other methods

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The high incidence of the relapses overstresses the shortcomings of gold therapy Only a small percentage of the relapses (about 10 per cent) were total, the majority yielding to further treatment Eighty per cent of the relapses had a duration of one year or less

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On the debit side, the following was shown·

1. About half of the cases responded only slightly or not at all to gold therapy.

2 Fatalities did not occur in our material, but an average of about 0 5 per cent is reported in the literature. In 36 per cent of the cases toxic reactions occurred during the first course and only slightly less frequently in the subsequent courses. However, only 6 7 per cent of these reactions were of a severe nature. The incidence and degree of the reactions corresponded closely to the average in the literature.

3. Relapses in the cases which achieved remission or marked improvement were high. In a five-year period of follow-up they amounted to about 60 per cent, and after ten years at least three-fourths of the cases had one or more relapses However, 90 per cent of the relapses were of less than one year's duration and only 20 per cent were stationary for over two years. A number of authors, among them Cecil, Boots, Ragan, Hartung and their collaborators, have likewise pointed out that most of the reactions are incomplete and amenable to further treatment. About 80 per cent of the patients who had significant improvement after the first course remained so for an average of four years out of a follow-up period of five, and seven years out of ten

CONCLUSIONS

On the basis of an evaluation of the favorable and unfavorable aspects, the answer to the third question is that gold therapy has a greater and more sustained ameliorative action on the inflammatory phase of rheumatoid arthritis than other means hitherto used. This conforms with the opinion of the majority of authors here and abroad Gold is not an ideal therapy from the standpoint of efficiency, toxicity and permanence. However, until a more efficient and less toxic agent is developed, continued use of gold is in order.

* * *

ABSTRACTS

THERAPEUTIC VALUE OF COPPER SALTS IN RHEUMATOID ARTHRITIS

JACQUES FORESTIER, A CERTONCINY AND F. JACQUELINE

Copper salts, as well as gold salts, are of therapeutic value in rheumatoid arthritis. The author has used two organic copper compounds· Cupro-allylthio-urea benzoate of sodium (Cupralene or Ebesal), which contains 19 per cent of copper, is water soluble, can be injected only intravenously, and has been used since 1942, and cupro-oxyquinoline sulfonate of diethylamine (Dicuprene), which contains 6 5 per cent of copper, is water soluble, can be injected either intramuscularly or intravenously, and has been used since 1945.

Animal experiments proved that the toxicity of copper was lower than that of [illegible] shorter than that [illegible]
[illegible]on,
[illegible]er-

age dosage of Cupralene has been 0 5 gm twice weekly, 6 to 12 gm. for a series, of Dicuprene, 0 25 to 0 50 gm twice weekly, 3 to 5 gm. for a series. Like gold salts, copper salts must be administered in repeated series with short rest intervals if prolonged action is desired.

Based on experience with over 300 cases, copper therapy is indicated in (a)

chronic polyarticular gout.

DISCUSSION*

Thirty-three cases of rheumatoid arthritis of varying duration were treated with Cupralene, the intravenously administered organic copper salt suggested by Dr. Forestier. Twenty-seven cases received adequate dosage and follow-up sufficient to be included in this report. A total dose of 10 gm was given to all twenty-seven

duration of their disease was from three months to thirteen years, with a mean duration of four years Thirteen patients had not received gold therapy and fourteen had received it, ten of whom had shown some improvement However, ten of these fourteen cases had developed a rash, anemia, or other toxic manifestation The other four had received full courses of chrysotherapy without benefit

There was no significant toxic effect if copper was administered in doses of 100 to 300 mg except for an occasional thrombosis in the punctured vein In doses of 500 to 1000 mg, toxic reactions were the rule and consisted of severe gastro-intestinal irritation marked to severe anemias, and occasional chills and fever Five hundred mg. was the maximum dose tolerated by the majority of patients

Of the twenty-seven cases, only two had complete remission, and both had had

and active, the patient had a complete remission of four months' duration after ten weeks of treatment and then relapsed again Of the other twenty-five cases, sixteen showed no improvement or were worse, and nine showed some improvement but just enough to be consistent with the variability of the disease

The incidence of remission of this series of cases treated with Cupralene was low Those remissions observed were extremely rapid and dramatic and the attendant hazards were considerably less than those of chrysotherapy

GOLD TOXICOLOGY AND RHEUMATOID ARTHRITIS, WITH PARTICULAR EMPHASIS ON BONE MARROW STUDIES

CHARLES LE ROY STEINBERG

One hundred and seven typical cases of rheumatoid arthritis were treated with gold thioglucose in oil The initial dose was 40 mg, followed the next week by 60 mg, in most instances 100 mg. was then given weekly by intramuscular injection

A total of 154 bone marrow aspirations were done on ninety of these patients The following toxic reactions were noted in the 107 cases treated. Thirty-two patients developed skin manifestations Four patients developed varying degrees of thrombocytopenia One patient developed maturation arrest of the granulocytes

* By Terence L. Tyson and Hilary Holmes

in the bone marrow. Ten instances of albuminuria with erythrocytes as a cause of albuminuria were noted in the 107 patients treated Two patients developed untoward gastro-intestinal symptoms and one patient developed hyperpyrexia. Thus, fifty instances of gold toxicity were noted in the group of cases treated

Eosinophilia of the bone marrow preceded the skin manifestations by several weeks, findings of 3 to 7 eosinophils per high power field were common In instances in which the peripheral platelet count dropped, a bone marrow aspiration was done. Gold treatment could be continued in those cases in which the bone marrow was normal, but had to be stopped if megakaryocytes and platelets were scarce

Severe instances of gold dermatitis responded well to BAL treatment. Gold treat- [illegible]

those patients who developed 3 or 4 plus albuminuria

Bone marrow aspiration is a simple procedure. The study of the bone marrow [illegible] patients receiving gold treatment. This laboratory pro- [illegible]

phase of gold toxicity

ORTHOPEDIC AND PHYSICAL TREATMENT AND STUDY

PREVENTION OF DEFORMITY IN THE HANDS IN RHEUMATOID ARTHRITIS

LORING T SWAIM

The hand is essential to successful living. Since its joints are involved in the very beginning of rheumatoid arthritis, it is important to understand the simple orthopedic measures which will prevent deformity if used early

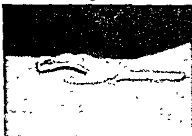

Fig 34


Fig 35


Fig 36

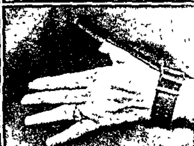

Fig 37

Fig [illegible]

[illegible]

The first essential is a strict watch of the hands from the very beginning The second is to apply splints at the first sign of contraction Where inflammatio
to preven
tion follo
positions
and are preventable

Splints correct bad position, relieve pain, and reduce swelling, and because protective spasm is no longer necessary to obtain comfort, subluxa-

tion of the joints does not take place. When splints have been used to rest the hand in good position ankylosis does not occur and better joint motion results

Following complete rest for three to seven days, guarded motion is started each day. If there is no reaction the hands are exercised daily for longer periods. At night the splints are always bandaged on in the correct position This procedure shortens the inflammatory period. However, the splints are continued at night for months until there is no danger of the relaxed joints' slipping, for night is a dangerous time during which bad positions may be taken in sleep.

The splints are made of plaster of paris bandage, rolled into a slab. This slab is applied to the palmar surface of the hand (Fig 34) from the tip of the fingers to the elbow and bandaged with gauze to the arm from the wrist up, assuring a good fit. The hand is held with the fingers fully extended, the palm flat and the wrist in a cocked-up position When dry, the plaster is trimmed and a space is left for the thumb, which does not deform like the fingers The splint is then firmly bandaged to the hand, thereby giving complete comfort and rest

A splint especially designed to prevent subluxation of the metacarpophalangeal joints is the clam shell The whole hand, with the exception of the thumb, is bandaged with plaster. While the plaster dries the hand is held firmly between the opposed hands of the operator, who squeezes the plaster flat. It is removed by cutting along the dorsum of the little finger, leaving a supporting edge, then the flap on the dorsum is lifted and the cast is removed to dry Space is cut for the thumb and the palmar side is trimmed to extend from the base of the hand to the first phalangeal joints [illegible]

tion, yet all the other finger joints can be used

The third splint (Fig 37) is for the thumb. It is of light steel held by a wrist strap which prevents subluxation at the carpometacarpal joints and *preserves the palmar arch. The distal end has a cap* which fits over the end of the thumb, thus keeping the thumb in line

If hands are splinted from the onset of rheumatoid arthritis serious deformity can be prevented.

° ° °

RECONSTRUCTIVE SURGERY OF ARTHRITIS

PHILIP D. WILSON

Reconstructive surgical procedures of different types may often be of great help in the treatment of patients with severe arthritic disabilities. It is necessary for physicians who have the responsibility for the care of arthritic patients to know the surgical indications and something about the benefits that may be obtained from operation in order that they may refer the patients at a time when the maximum benefits from surgery may

be obtained The indications for operative treatment are quite limited and nothing but failure will result if they are disregarded They apply only to joints which show serious damage of an irreversible type Surgery should never be considered in arthritic disabilities where there is possibility of improvement from medical treatment.

In general terms the disabilities that call for surgical consideration may be stated as persistent painful joint function which is unrelieved by general and local treatment, fixed flexion contractures of the joints, other disabling types of joint deformities, and ankylosis, either fibrous or bony, which seriously handicaps the patient Many different operative procedures may be used in overcoming these conditions but they are chiefly described in the following terms arthrotomy, synovectomy, patellectomy, exostectomy, bony resection, osteotomy, arthrodesis and arthroplasty

It is of the utmost importance when considering surgery to differentiate between the various forms of arthritis, since the indications for operation are different in each type and the response and prognosis are also different We classify the various forms as gouty arthritis, osteoarthritis, rheumatoid arthritis and Marie-Strumpell spondylitis, and we will consider each type separately with respect to surgical treatment

GOUTY ARTHRITIS

The only indication for surgery in gouty arthritis is the removal of tophus deposits which, on account of their location, interfere with the function of an extremity or which, by reason of ulceration or drainage, threaten the danger of invasive infection The most common locations of such deposits are in and about the metatarsophalangeal joints, the malleolar prominences, the tendo achillis, and overlying the patellae in the lower extremities and overlying the olecranon processes or in and about the fingers in the upper extremities Only a small percentage of patients who suffer from gouty arthritis develop tophus deposits of this type, but when they occur they may be very troublesome, particularly in the feet Here, if they are on the plantar surfaces, they are subjected to continual trauma from weight bearing, if they develop on the dorsal surface of the foot or about the metatarsophalangeal joints of the first or fifth toes or about the heel, they are exposed to shoe pressure

The eventual result when left untreated is that the deposit causes ulceration of the overlying skin and sinus formation with drainage of serous fluid and tophus material This is followed by infection with recurring attacks of cellulitis and lymphangitis I have personally encountered several cases in which the tophus infiltration resulted in extensive bony destruction accompanied by ulceration and chronic infection In one case there was complete loss of the first, second, and third metatarsals which had been replaced by deposits of tophic material

Surgical treatment necessitates the removal of as much of the tophic deposit as possible with obliteration and closure of the space which it occupied and primary suture of the overlying skin As far as the surgical results are concerned, the patients are generally quite satisfied from the removal of the tophi While slow recurrence of the deposit may be expected it is generally a matter of years before it can resume its previous proportions I cannot recall any case in which it was necessary to reoperate at the previous site On the other hand, I have had to reoperate in several

cases because of the enlargement of other deposits which were small at the time of the original operation

OSTEOARTHRITIS

The more common and severe manifestations of osteoarthritis are encountered in a single joint or in similar joints of the two extremities. They are generally the result of congenital malformations of the two components of a joint, often bilateral, or of acquired deformities which may be due to disturbances of the epiphyseal growth centers, or to infections, fractures or avascular necrosis It may be stated as a general rule that any condition which leads to incongruity of the articular surfaces or to abnormal stresses of force and strains on a normal joint, when acting over a period of years, will result in the development of osteoarthritis.

The osteoarthritic process consists chiefly in the wearing away of the joint cartilages, the condensation and eburnation of the underlying bone and the reactive development of bony spurs or osteophytes at the margins of the articular cartilages The process may be accompanied by the formation of loose cartilaginous bodies in the joint resulting chiefly from metaplasia of the hypertrophic synovial villi and subsequent detachment. Features of outstanding importance in the understanding of the process are the absence of osteoporosis and the nonoccurrence of ankylosis, either fibrous or osseous.

Since the osteoarthritic reaction tends to be aggravated by abnormal strains or by trauma, it follows that the weight-bearing joints of the lower extremities and of the spine are those that are most frequently implicated and the indications for surgical intervention arise chiefly in the knees, hips and ankles, in that order, either singly or bilaterally, and also in the spine It is unusual to encounter any osteoarthritic manifestations in the upper extremity that requires surgery except rarely following fractures Contrary to the situation that prevails in rheumatoid arthritis, the surgeon is called [illegible] one or two [illegible] di- [illegible] he [illegible] he [illegible] problems of senescence must often be faced One of the most difficult questions that must be answered is how to give relief of pain to a patient whose general condition is too poor to permit carrying out the type of procedure which is most likely to solve the problem

The Knee PATELLOFEMORAL OSTEOARTHRITIS. One of the most common causes of osteoarthritis of the knee is subluxation of the patella. Many different factors may have played a part in the displacement, such as faulty alignment of the quadriceps extensor mechanism, a poorly developed trochlear ridge on the lateral condyle of the femur, moderate genu valgum deformity or an early untreated chondromalacia of the patella All of these cause unusual wear on the patellofemoral cartilage, with reactive osteoarthritis Recognition of the condition is not difficult on clinical examination, which discloses enlargement of the patella, marked crepitation on movement of the patella and evidence of joint irritation The roentgenographic examination may show some evidence of generalized osteoarthritis but there is marked narrowing of the patellofemoral cartilage space, whereas the tibiofemoral cartilage spaces are well preserved

In these cases partial or complete patellectomy should be done At the same time care should be given to the removal of such other abnormalities in the joint as may constitute sources of pain or impediments to function, such as osteophytic spurs, villous hyperplasia of the synovial membrane or hypertrophy of the infrapatellar fat pad. In the older patients complete removal of the patella is to be preferred but in the younger patients it is often better to leave a small superficial layer of the patella in order not to weaken the quadriceps extensor mechanism, but in this case the raw undersurface of the patella should be covered with a synovial flap In the older patients it is particularly important to begin exercise of the knee within two to three days and weight-bearing at the end of one week

LOOSE BODIES In many cases of osteoarthritis of the knees, loose bodies develop as a result either of synovial budding and metaplasia or of fracture of an osteophytic spur In some cases there may be extensive osteochondromatosis. In the latter cases synovectomy, as complete as possible, is generally required, in the former, it is generally sufficient to perform an arthrotomy and remove only the loose bodies. It is important when evaluating the indications for surgery to be sure that the patient's disability is due to the loose bodies and not to the associated osteoarthritis

GENERALIZED OSTEOARTHRITIS The question of determining if surgery should be undertaken in cases of generalized osteoarthritis of the knees will depend upon whether the condition is bilateral or unilateral and whether the antecedent cause of the osteoarthritis can be discovered and remedied For example if the process is unilateral it is likely that some intra-articular cause may be discovered and eliminated, such as a torn meniscus, a hypertrophied fat pad or a chondromalacia of the patella If there is a considerable flexion contracture there may be a bony block to extension that can be released. When there is chronic effusion in the joint the removal of the thickened and hypertrophied synovial membrane may give relief If there is a popliteal cyst this should be removed since such cysts commonly communicate with the knee joint and, when traumatized and inflamed, may give rise to an intermittent synovitis

When the osteoarthritis is bilateral and there is an obvious disalignment of the limbs with either genu valgum or genu varum which, from the roentgenographic evidence, is the causative factor, then the limb should be straightened by osteotomy whenever possible I have observed marked diminution in pain and improvement of function even when such corrective measures are carried out in middle age or later

The Hip. From a surgical standpoint one of the great controversial questions is what to do for osteoarthritis of the hip with limited and painful function The answer varies and depends upon the age and sex of the patient, the condition of the adjacent joints and whether the process is unilateral or bilateral When there is severe disability the choice of the surgical procedure which may be employed includes subtrochanteric osteotomy, acetabuloplasty, arthroplasty and arthrodesis When the patient's general condition is not good enough to permit these procedures, then the surgeon may elect to employ Tavernier's method of dividing some of the sensory nerves supplying the joint, or to carry out a simple nail fixation of the joint with a view to obtaining temporary relief of pain

It may be said of subtrochanteric osteotomy that it is a method for correcting deformity of the joint, as when the limb is in a fixed position of

flexion and adduction with reference to the body. It improves the standing posture, corrects *relative shortening of the limb* and allows the patient to walk better. It does not alter the pathologic condition within the joint and there may still be complaint of pain on movement except in unusual situations when the change in alignment of the limb causes a shift of forces acting on the articular surfaces which relieves pressure and pain In my judgment the operation should be reserved for cases of old congenital subluxation and others where there is a marked flexion adduction deformity of the hip In other cases there is a tendency for the limb to drift back into the old position of deformity after a time with recurrence of the original complaint

Acetabuloplasty is of value chiefly in conditions when the femoral head is buried deeply in the acetabulum, as in protrusio acetabuli or Otto's pelvis This operation aims to remove the bony spurs at the anterior and lateral margins of the acetabulum which impede the motion of the hip, and also to remove the anterior portion of the capsular ligament and synovial membrane It is of little or doubtful benefit except in the condition described above

Arthroplasty, or the making of a new joint, is an operation that makes a powerful appeal to a patient with an osteoarthritic hip. Quite naturally he anticipates that the new joint will be like the normal hip and the surgeon *has a difficult task in disillusioning him in this respect and in trying to give* him an accurate picture of what he may expect in the way of function In our experience with arthroplasty of the hip in osteoarthritis at the Hospital for Special Surgery, the results were considered excellent or good in twenty-one patients (61 per cent), poor in ten (30 per cent), and fair in 10 per cent In a follow-up study of thirteen fascial arthroplasties with a view to comparing them with the mold arthroplasties, we found the results were excellent or good in nine (69 per cent), fair in two (16 per cent), and poor in two (16 per cent) The results were similar irrespective of whether the arthroplasty was performed with the aid of a vitallium mold or with fascia lata From the surgeon's standpoint the operation is easier when the mold is used because the patient is spared the additional operation of obtaining the fascia lata and less time is required

From my own experience I conclude that the results of arthroplasty are not predictable with accuracy When the condition is bilateral and there is much limitation of motion and severe disability, then arthroplasty is to be advised When the condition is unilateral and the patient is a woman I advise arthroplasty because generally she can regulate her activities better than a man and from a social standpoint a comfortable sitting posture is more important than being able to stand and walk a good deal But I explain to her that she will walk with a limp and that generally she will want to use a cane when she walks outside If the patient is a man whose spine and other hip are normal, and if he wants to lead an active life, I advise an arthrodesis

Fusion of the hip, or arthrodesis, is the operation of choice for a man of any age who wants to be active and on his feet a great deal When the spine and other joints are normal and the fusion is performed with the limb in optimum position, the patient can walk with scarcely any trace of limp, is entirely free from pain and may be as active as he pleases. *The sitting* posture may be awkward but the patient has little difficulty in driving a

car. As between the period of time required for postoperative treatment following arthrodesis or arthroplasty, there is little difference as far as hospitalization is concerned. Generally the patient with an arthrodesis will be free of treatment at the end of six months while the patient with arthroplasty will still be working with exercises and requiring supervision up to the end of a year.

As for the Tavernier operation of sectioning the sensory nerves to the hip, chiefly the obturator and the nerve to the quadratus femoris, our own experience is small but it includes patients who have continued to complain of pain following operation without much relief It seems to me that this operation is indicated chiefly in two classes of patients. first, those who preserve a satisfactory range of motion in the hip but complain of pain, and second, feeble, elderly patients who are unable to endure any more serious procedure.

Simple fixation of the hip by passing a nail through the femoral head into the pelvis is a method of giving temporary relief of pain It cannot, except in rare instances, bring about true ankylosis and inevitably the nail will loosen in the course of time and require removal The last patient in whom I performed this operation fractured her femur in the subtrochanteric region when she first tried to stand She secured union of her fracture after immobilization in plaster for three months but the fact that she survived this treatment proves that she might just as well have survived an arthrodesis. I am told that Sir Reginald Watson-Jones, who devised this method of treatment, has given it up more or less completely I conclude, therefore, that it has only a limited indication

Other Joints There are other joints in which osteoarthritic conditions can be relieved by surgical treatment but these are chiefly following fractures or infectious processes, such as, for example, the ankle, shoulder and wrist In these joints arthrodesis is the solution of choice and, provided that the operation is carried out in a manner to fix the joint in the optimal position, excellent function can be obtained In these joints arthroplasty is of no value

In
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with the humerus in 60 degrees abduction, about 15 degrees of external rotation and about 15 degrees of forward elevation These patients can bring their hands to their mouths or any part of their heads and can carry out every function except that of reaching to their backs As long as the opposite shoulder is normal they have no sense of handicap. As far as the wrist is concerned, ankylosis in the position of 15 degrees dorsiflexion or extension at 195 degrees causes no sense of disablement as long as pronation and supination of the forearm are preserved and there is normal use of the thumb and fingers Most patients feel that it is a cheap bargain to purchase relief of painful disability at the wrist by sacrifice of the wrist motions.

RHEUMATOID ARTHRITIS AND ANKYLOSING (MARIE-STRÜMPELL) SPONDYLITIS

From the standpoint of reconstructive surgery, the most difficult problems are met in rheumatoid arthritis. Here the surgeon has to deal with a generalized disease whose chief visible manifestations are in the joints

Because of the obvious articular involvement and the absence of other symptoms it is easy to overlook the well known fact that the disease process also implicates the muscles, the connective tissue structures and the viscera Here if the surgeon undertakes an operation that is obviously indicated to mobilize an ankylosed joint and obtains a satisfactory anatomical result, he may be defeated by his inability to obtain the cooperation of the muscles and other soft tissue structures which control movement.

The pathologic process in the joints is characterized by synovial proliferation which leads eventually to pannus formation and destruction of the articular cartilages It frequently results in fibrous or bony ankylosis. An outstanding feature of the process is osteoporosis of the bony structures leading to softening of the bone in the subchondral and epiphyseal regions and ultimate collapse of the osseous structures which support the joint surfaces. Even when there is bony ankylosis the osseous structure is often soft, with atrophy of the trabeculae and replacement by fibrous and fatty elements.

The course of the disease is slow and chronic and is characterized by periods of progression and activity followed by remissions with periods of quiescence, so that it is difficult to know whether at any given time the disease is arrested Nevertheless, I have seen enough cases in which the arrest has been permanent over a period of years to prove that this can occur and the operative results in these cases have been sufficiently better from a functional standpoint to convince me that the optimum time for operative treatment is when the disease is quiescent. On the other hand, the surgeon sees many severely crippled patients, with severe joint damage which can only be improved by surgery, in whom the signs of activity of the disease continue more or less indefinitely. Here the surgeon has to make the choice of operating in the active phase or of condemning the patient to indefinite invalidism If the nature of the situation and the surgeon's difficulties are explained to the patient, he is generally willing to take the gamble of operative treatment because in the last analysis he has nothing to lose.

Another feature that complicates the problem of giving the patient relief by surgery is that many joints are involved in the disease. In one patient the surgeon may have to deal with limited function in both upper and lower extremities If he undertakes to restore function to the hip the painful and limited motion of the knee may seriously interfere with obtaining a satisfactory result The pattern of the disease varies greatly, however, in different patients and often there is major involvement of only one joint in an extremity with relatively satisfactory function in the other joints Such a situation creates a relatively favorable indication for reconstructive surgery.

In considering these complicated cases with a view to determining whether surgery can be of help it is necessary to simplify the problem as much as possible This may be accomplished by considering the functional objective that one desires to obtain and whether or not, in view of other handicaps that are present, this is worth the trouble and effort required of the patient.

Upper Extremity Here the chief objective is to make it possible for the patient to take care of himself even if confined to a chair or bed, and the key to improvement is generally the elbow Even though the hand is seriously involved some power of grasping is generally preserved although it

may be only a pinching action between the thumb and index finger. There may also be limitation of shoulder movement, but some elevation of the

elbow by operation the surgeon makes it possible for the patient to convey food to the mouth, to dress himself, and to perform many other needful and useful tasks.

Lower Extremity. The chief objective with regard to the lower extremity is to make it possible for the patient to move about by the use of his own powers of locomotion This necessitates not only the ability to walk with or without crutches or other aids but also to be able to arise from and sit down again in a chair without help Without these latter functions the ability to walk is of no value because the patient is still dependent upon help from others

When considering the possibility of restoring locomotion by operative treatment the key joints are the hips and knees When the hips are stiff and the knees are good the prospects are favorable When the hips are good and the knees are bad, it is frequently possible to improve the situation If both hips and knees show limited function then the outlook for improvement as a result of surgery is poor and it is improbable that the surgeon can ever restore the power of locomotion In these combined hip and knee deformities the ability to sit comfortably is generally more important than the ability to stand erect The surgeon should be cautious when tempted to straighten flexed joints in these circumstances because he may convert a good sitter into a patient who can only be extended in bed When in these cases the patient is young and the indications are unusually favorable, then a compromise between the sitting and standing posture is generally advisable. The surgeon may undertake operations to mobilize the hips but he should aim for semiflexed positions of the knees or perhaps one knee straight and the other partially flexed

Upper and Lower Extremities Combined When the patient is handicapped by disabilities affecting both the upper and lower extremities the improvement of the uppers should generally take precedence over the

value.

Operations in Rheumatoid Arthritis and Marie-Strümpell Spondylitis

Synovectomy of the Knee The results of synovectomy of the knee in rheumatoid arthritis are variable and depend in large part upon the amount of joint damage that is present. In general, pain is relieved but the range of motion is diminished Removal of the patella as a part of the operation does not, in my experience, improve the results. I believe the indications should be restricted to the cases with marked joint swelling and effusion, where pain is a prominent feature. It should not be done for the purpose of correcting flexion deformity of the knee.

Treatment of Flexion Deformities of the Knees Flexion deformities of the knees are exceedingly common in rheumatoid arthritis and require

orthopedic treatment. They arise generally as a result of the patient's effort to maintain the joints in a relaxed position where pain is minimal. Gradually the muscles become contracted and the joint ligaments lose their elasticity and become fixed in the shortened position Secondary erosion of the articular cartilages takes place in the areas subjected to pressure so that after a time there develops a bony block to extension Additionally the patella becomes bound down to the femur by adhesions so that the function of the quadriceps extensor mechanism is impeded

What can be done to extend the knees will depend largely upon the extent of knee damage In the early cases simple weight and pulley extension with adhesive plaster may suffice When correction is obtained then bivalved plaster splints may be used part time to prevent recurrence. Prolonged fixation of any rheumatic joint in plaster is inadvisable because it generally leads to loss of motion, in the treatment of these flexed joints it is important to combine exercises and activity, when possible, along with corrective treatment For this reason one must be cautious in employing wedging plasters or hinged plasters or any of the host of appliances that have been contrived for the purpose of obtaining extension of the knees.

When the flexion deformity is of long standing, operative correction will probably be required The operation of posterior capsuloplasty which I have described is valuable when the amount of articular damage is slight. This operation is designed to strip away the upper attachments of the posterior capsular ligaments to the femur and thus allow extension of the knee If the hamstring muscles are very contracted, one or more of them, generally the biceps femoris, may be lengthened In severe deformities it is sometimes necessary to divide the medial and lateral collateral ligaments Following operation, the knee is immobilized in plaster in the extended position for a period of two weeks after which exercises are started.

When the patella is adherent and prevents action of the extensor muscles of the thigh, patellectomy is generally required This may be combined with posterior capsuloplasty when necessary

When the flexion deformity of the knee is of long standing and is associated with considerable articular damage but the patient still retains an active range of motion in flexion, then an osteotomy of the femur above the condyles may be indicated After the femur is divided the knee is extended by rotating the condylar fragment forward The lower extremity must then be splinted until healing of the fracture is obtained Bearing in mind the harmful effect of long continued splinting of rheumatic joints, it is important for the surgeon to employ internal metallic fixation of the fragmen [illegible] order to reduce the period of splinting and to permit [illegible]

A [illegible] ankylosed joint is of great value in the surgical treatment of rheumatoid arthritis It is most successful in ankylosis of the temporomandibular joint, the elbow, the hip and lastly the knee and in that order.

THE TEMPOROMANDIBULAR JOINTS When there is ankylosis of the mandibular joints with inability to open the jaw or to separate the teeth, then an operation should be performed to mobilize these joints. Generally all that is necessary is to resect the condylar process and to leave a wide space between it and the temporal bone Fascia may be interposed to prevent re-ankylosis but probably this is unnecessary if the intervening space between

the bones is wide Generally the ankylosing process is bilateral and it is necessary to carry out the operation on both sides This may be done in two stages or on both sides at the same time Postoperative treatment by exercises to stretch the muscles and increase mobility is most important and is started within a few days

When other reconstructive operations must be done on a patient with mandibular ankylosis, arthroplasty of the jaw should have first priority in order to diminish the risk of anesthesia and to make possible the opening of the jaws and the expulsion of vomitus

THE ELBOW Arthroplasty of the elbow in rheumatoid arthritis has been most successful, in my experience, in restoring a useful range of motion There has been some controversy in the past over the relative merits of arthroplasty compared with resection of the elbow The latter procedure gives good function in a patient who has good muscular development, where muscle power can make up for lack of stability. In patients with rheumatoid arthritis, however, the muscular power is poor and it is necessary to remodel the bony structure in order to provide stability Interposition of a double fascial layer serves to prevent reankylosis and also forms a fibrous layer between the bones, which is favorable for the development of a condition resembling pseudoarthrosis which permits motion If there is loss of the rotary movements of the forearm, resection of the radial head is required, and if there is arthritic involvement of the inferior radio-ulnar joint then resection of the distal end of the ulna must also be done

Postoperatively, the elbow is immobilized in plaster for two weeks, following which exercises are started with the forearm supported in a sling Passive movement and stretching are not advisable and I believe chief reliance should be placed on active exercises and occupational therapy.

vitallium mold arthroplasty in 1939 this method has had the preference.

Our own experience with vitallium mold arthroplasty has not been too encouraging and the results in rheumatoid arthritis are less favorable than in osteoarthritis Of twenty-five patients who were operated upon by this method and followed, there were no results that were classified as very good and only eight (32 per cent) were considered good The results were poor in twelve (48 per cent) and the remainder were fair The causes of failure were chiefly absorption of the femoral neck due to avascular necrosis, and loss of motion due to cicatricial or bony overgrowth There was occasional subluxation of the hip.

Reankylosis occurred in some of the cases of rheumatoid spondylitis These cases exhibit a great tendency to ossification of soft tissues and I have also observed some cases in which reankylosis occurred even when there had been a wide resection of the head and neck of the femur

When wide resection is carried out and the result is favorable, good mobility is obtained but there is considerable instability Such patients have to use crutches in walking but this is a small price to pay for regaining the power of locomotion Batchelder has attempted to improve stability of the hip by performing a subtrochanteric osteotomy after resecting the head

and neck of the femur, but this would seem to be unnecessary in rheumatoid arthritis.

While the results of mobilizing operations upon the hips in this disease cannot be considered as exceptionally favorable, I believe we *should continue* to employ these operations in cases of bilateral hip ankylosis, *particularly* when there is also an ankylosing spondylitis because otherwise the patients are condemned to confinement to bed

THE KNEE. Arthroplasty of the knee is successful in overcoming ankylosis *only in* cases where the condition is the result of old gonorrheal or septic *arthritis* or of traumatic conditions. This operation usually fails in rheumatoid arthritis although occasionally a satisfactory result is obtained The good results will only be obtained when osteoporosis is lacking and the bones show good density.

Miscellaneous Operations. SPINAL DEFORMITY. The correction of spinal deformity is strongly indicated when the spine is ankylosed in a position of flexion and the patient is unable to assume an erect posture This deformity is encountered chiefly in patients with rheumatoid spondylitis, and there may be associated flexion deformities of the hips which still further increase the flexed posture in which the patient walks.

Correction is carried out by osteotomy through the articular processes, as described by Smith-Petersen, with such additional osteotomy through the laminae as may be necessary to allow extension of the spine This procedure is carried out at several different vertebral levels in the lumbar spine and then, by extending the operating table, the patient's spine is also extended A bone graft may be introduced to obtain fixation or the body may be supported in a plaster shell or jacket.

This operation is indicated only when the ankylosing process is situated in the posterior elements of the spine and when there is little or no ankylosis between the vertebral bodies

ARTHRITIC DEFORMITIES OF THE FEET Fixed equinus deformity of the feet in rheumatoid arthritis is generally due to ankylosis at the ankles or posterior tarsal joints. When it is impossible for the patient to get his feet flat upon the floor in standing or walking, there is considerable disability and the deformity should be corrected. This generally necessitates a wedge osteotomy or resection through the ankle or subastragalar joint

Another painful deformity of the feet in rheumatoid arthritis is hammer toe deformity of several or all of the toes of both feet This is usually associated with painful calluses under the metatarsal head and it is impossible for the patients to stand or walk with comfort. The best method of giving relief in these cases is to resect the proximal half of the proximal phalanx of the great toe and the proximal phalanges of all of the lesser toes This corrects the toe deformities and allows shoes to be worn with comfort When there is continued complaint of pain from pressure on the heads of the metatarsals then these must also be resected

LIMITED FUNCTION OF THE SHOULDER Stiffness or ankylosis of the shoulders does not as a rule cause great disability as long as there is freedom of scapular movement. When the acromioclavicular or sternoclavicular joints become ankylosed then scapular motion is lost and the shoulder becomes rigidly fixed. In such cases resection of the distal end of the clavicle restores mobility of the scapula with very satisfactory improvement of shoulder function

M. N SMITH-PETERSEN

Since there is nothing to be gained by discussing the points on which Dr Wilson and I agree, I shall confine my remarks to those aspects of his paper with which I do not agree

In treating osteoarthritis, arthrodesis is never indicated, no matter what the patient's age or occupation may be If a patient can survive the operative procedure of arthrodesis and the postoperative treatment of immobilization, he certainly can survive a mold arthroplasty without postoperative immobilization

Arthrodesis does not always result in bony ankylosis, it is not uncommon that a second attempt has to be made to bring about the desired result. Cases have been reported in which even a third attempt has been necessary

In 111 arthroplasties of the hip for osteoarthritis a revision was indicated in five instances These were all performed during the early period of mold arthroplasty, when our technique was more faulty than it is at the present time

The functional result of mold arthroplasty should be such that the patient can return to an occupation consistent with his physical age

An ankylosed hip demands compensatory function of the spine and all the j

rise

prod

to say the least, limit the patient's activities I believe that it takes longer than six months to achieve an unquestionably bony ankylosis, to limber up stiff joints, to restore muscle power

Dr Wilson further states "The patient with an arthroplasty will still be working with exercises and require supervision up to the end of a year" He is absolutely right, although it may take longer than a year, or even several years What objection is there to exercises if they do not interfere with activities and earning a living? Some of us do setting up exercises for the sake of keeping well, arthroplasty patients do exercises for the sake of acquiring a joint that will improve with age They have a real incentive for doing chores

In discussing surgery of the upper extremity in the treatment of rheumatoid arthritis, Dr Wilson states "The key to improvement is generally the elbow" A complete arthroplasty is not always indicated By interpretation of subjective pain and physical findings it is often possible in the early stages of the disease to localize the chief source of disabling pain to the radiohumeral articulation By excision of the radial head and surrounding synovialis, the joint between the humerus and the ulna can be made to function quite satisfactorily

We are very happy about the relief of pain resulting from excision of the acromion It relieves pain arising from the subacromial bursa and allows relatively pain-free compensatory scapulothoracic motion This operation does not result in a marked increase in glenohumeral mobility, but it does improve function because of the pain-free compensatory motion between scapula and chest Again this operation must be undertaken only after careful interpretation of subjective pain and physical findings

"Vitallium mold arthroplasty of the hip has not been too encouraging, and the results are less favorable than in osteoarthritis." Let us keep in mind that we are operating under most unfavorable conditions: bone atrophy and muscle atrophy, and loss of elasticity of fascia and intermuscular septa Until partial, relatively pain-free function is restored such conditions render the chances of a favorable operative result improbable. For this reason we have had to resort to revisions of the primary arthroplasty in two to five years in twenty-three instances out of a total of 153 cases. The revisions have achieved satisfactory improvement in range of motion and consequently increasing activities.

It has not been our experience with mold arthroplasty that absorption of the femoral neck and head is the chief cause of failure It certainly was a common experience in fascia lata arthroplasty.

* * *

BONE ABSORPTION IN RHEUMATOID ARTHRITIS*

The Opera-Glass Hand (La Main en Lorgnette)

CHARLEY J. SMYTH

In 1913 Marie and Léri[1] reported the case of a seventy-year-old woman with advanced destruction of cartilage and bones of the hands Her severe polyarthritis had set in twenty-eight years earlier and also involved the

Table 35 Previously Reported Cases of the Opera-Glass Hand or La Main en Lorgnette

AUTHORS		PATIENT'S AGE	SEX F	SEX M	POLYARTHRITIS	DURATION OF ARTHRITIS, YEARS
Marie and Léri[1]		70	F		Yes	28
Weigeldt[2]		64	F		Yes	18
Sturshberg[3]		53	F		Yes	37
Nelson[4]		31	F		Yes	19
Crain[5]		55		M	Yes	13
Nielsen and Snorrason[6]	Case I	43	F		Yes	17
	Case II	55	F		Yes	50
	Case III	56	F		Yes	23
	Case IV	48	F		Yes	13
		Avg age 53	8F	1M	All	Avg 24

elbows, shoulders, hips and vertebral column. The severe bone absorption in the hands at the metacarpophalangeal and interphalangeal joints permitted the telescoping of one bone upon the next. The skin over the finger joints was invaginated with ringlike folds To this deformity was given the name "la main en lorgnette" (the opera-glass hand) because the transverse folds of skin of the fingers resembled a folded telescope.

Only eight additional cases of this syndrome have been published, these are listed in Table 35

* From the Medical Departments of Wayne University College of Medicine, Detroit and the Wayne County General Hospital, Eloise, Michigan

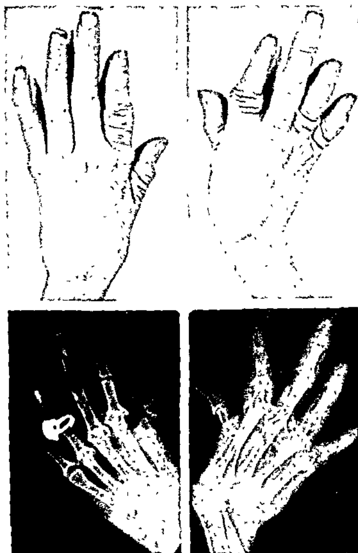


Fig 38, Case I Photographs and roentgenograms of the hands of a thirty-two-year-old woman The roentgenographic changes include extensive osteoporosis, resorption of carpal bones and distal ends of the radius and ulna The heads and most of the shafts of the proximal phalanges (2 4 and 5) are resorbed, with evenly rounded distal ends The head of the first metacarpal shows partial dissolution, with the proximal end of the first phalanx hollowed out to receive the rounded end of the metacarpal. The proximal interphalangeal joint of the middle finger shows bony ankylosis of the type seen in rheumatoid arthritis Changes in the left hand are similar






Fig 41, Case II Photographs and roentgenograms of the hands of a Negro woman, age sixty-six, showing typical opera-glass hand deformities in all fingers




Fig 42, Case II Roentgenograms of both knees, posterior-anterior projection, and a lateral view of the left ankle, showing bony ankylosis of these joints.

both ulnae The heads of the metacarpals and proximal phalanges were small and fit into the cup-like excavation of the adjoining bone. Roentgenograms of both knees and the right ankle (Fig 42) showed complete loss of articular space and bony ankylosis Laboratory studies revealed a moderate anemia, but were otherwise negative.

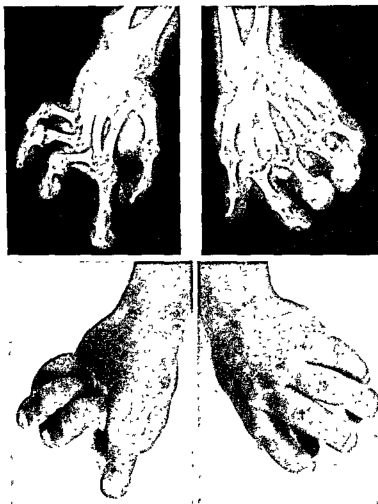


Fig 43, Case III Photographs and roentgenograms of the hands of a thirty-three-year-old white man who had had rheumatoid arthritis since age five Atrophy and subluxation of the metacarpophalangeal joints are illustrated

Case III This patient was a white man admitted when twenty-three years old, with Still's disease He died at the hospital ten years later He lived a restricted life with little discomfort due to the widespread deformities and fused joints Exam[illegible] and roentgenograms [illegible] small [illegible]
[illegible]



Fig 44, Case III *Photomicrograph of a section taken from the left fourth metacarpophalangeal joint, showing partial absorption of the head of the metacarpal and invagination into the base of the phalanx, with dense fibrous and fatty tissue displacing bony trabeculae*

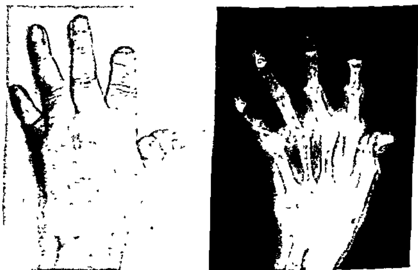


Fig 45, Case IV Photograph and roentgenogram of the left hand of a fifty-eight-year-old white woman, showing deformities of all fingers Bone absorption is most marked in the thumb and fifth finger Other changes characteristic of advanced rheumatoid arthritis are present

fifth right fingers were dislocated and hyperextended The laboratory data were compatible with the diagnosis of Still s disease The cartilage and underlying cortical bone is replaced and held together by acellular fibrous tissue and fat The remaining bony trabeculae were thin and the compact bone showed marked atrophy Sections taken at autopsy from the left metacarpophalangeal joints are illustrated in Figure 44



FIG 46, Case IV Roentgenogram of the left hip joint showing advanced destructive changes The head of the femur is small and irregular and the acetabulum is pushed into the pelvis, producing a unilateral, so-called "Otto pelvis"

The fingers of the left hand were short (Fig 45) and flail like, having deep creases in the skin overlying the proximal interphalangeal joints All of the features

about half normal size and the cortical surface was irregular The wall of the acetabulum was pushed into the pelvis, producing the condition of unilateral protrusio acetabuli ("Otto pelvis") A large number of laboratory studies were all negative except for the persistently elevated erythrocyte sedimentation rate

THE TELESCOPIC FINGER (DOIGT EN LORGNETTE)

In the original report by Marie and Léri[1] describing their polyarthritic patient with the "opera-glass hand," there was a brief reference to another

case having polyarthritis with destructive changes of bone involving only the joints of a single finger. To this condition the term "doigt en lorgnette" (telescopic finger) was applied. This same term had been used by Brumpt[7] in 1906 to describe the fingers of a Negro patient with progressive muscular atrophy, and he included sketches depicting these changes Nielsen and Snorrason[6] have subsequently referred to two cases with chronic rheumatoid arthritis having osseous destructive lesions limited to the joints of one digit. For some reason the cases with changes in only one finger have



Fig 47. Case V Serial roentgenograms of the right index finger showing progressive [illegible]
Arbor, Michigan)

received less attention than those with like structural changes in all five fingers

During the past several years we have been impressed with the high frequency of absorptive changes in the roentgenograms of finger joints of patients with advanced rheumatoid arthritis In a survey of the material from this hospital the following examples have been selected to illustrate the varying degree of joint destruction resulting from the marked lytic process of bone which has accompanied the loss of articular cartilage usually considered as a part of this disease.

Case V C W, a white woman, age thirty-four, developed typical rheumatoid arthritis involving the ankle, knee, elbow and hand joints when she was twenty

years of age. This patient has been examined at frequent intervals during the past fourteen years, during which time the disease has been active and progressive. Roentgenograms of the right hand taken at the first, seventh, ninth, and fourteenth year of the disease illustrate the gradual progressive destruction of joints of the right index finger (Fig 47). There was first a loss of the interarticular space of the index finger at the metacarpophalangeal joint, indicating cartilage destruction At the ninth year of the disease loss of bone substance was apparent, by the fourteenth year still further destruction had occurred and the head of the first metacarpal had become small, irregular and cystic and fitted into the cuplike excavation of the adjacent phalanx

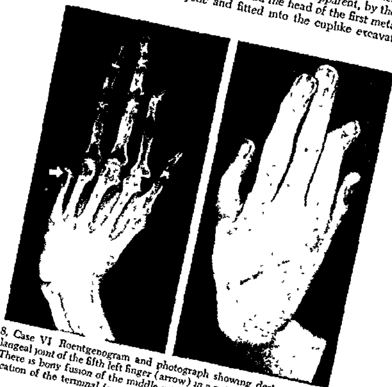


Fig 48, Case VI Roentgenogram and photograph showing destruction of the metacarpophalangeal joint of the fifth left finger (arrow) in a patient with advanced rheumatoid arthritis There is bony fusion of the middle interphalangeal joint and absorption of bone with dislocation of the terminal joint of the index finger

Case VI W. H., a man, age thirty-nine, had a typical rheumatoid arthritis involving multiple joints His illness began twelve years prior to the first examination when he was almost totally incapacitated The fifth left finger was hypermobile while the remainder of the fingers of this hand had restricted motion and many of the joints were ankylosed Roentgenographic examination revealed complete fusion of the middle interphalangeal joint of the index finger with absorption and dislocation of the terminal joint of this finger Both bones forming the joint of the base of the fifth finger were completely absorbed (Fig 48)

Case VII E G, a forty-two-year-old white man with late rheumatoid arthritis, had been studied six years before Roentgenograms taken at the time of the first examination revealed partial subluxation of the proximal phalanx of the thumb (Fig 49A) Six years later this same joint was completely dislocated and the bones composing these same joints show further dislocation and there was atrophy of bones of the fourth and fifth fingers (Fig 49B and C)

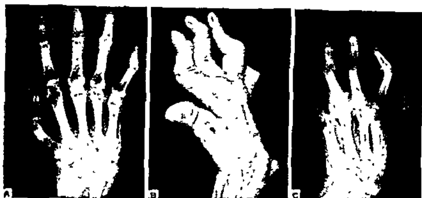


Fig 49, Case VII. A Roentgenogram of the right hand of a forty-two-year-old man, showing the changes of early rheumatoid arthritis There is partial subluxation of the proximal phalanx of the thumb B, C The same hand six years later, showing further involvement of the interphalangeal joints of all fingers There is complete subluxation of the thumb and partial subluxation of the interphalangeal joints of the fourth and fifth fingers, with advanced absorption of bone in these articulations

Fig 50 Roentgenograms of wrist joints of five patients with long standing rheumatoid arthritis In four of these patients the opera-glass hand syndrome was present

COMMENT

One finding of unusual interest in several of the reported cases of rh matoid arthritis in which bone absorption has been a prominent featu has been the roentgenographic evidence of a tapering deformity of th distal end of the ulna Weigeldt[2] in 1929 was the first to call attention t this change in a patient having the typical opera-glass hand, both ulnae were cone-shaped at the lower end like the point of a pencil This roentgenographic appearance has been reported to exist bilaterally in one case by Stursberg,[3] in another by Nelson[4] and in two cases described by Nielsen[5] In Figure 50 are reproduced the roentgenograms illustrating this condition, four of these represent cases of opera-glass hand being reported and the fifth



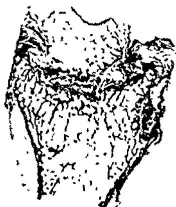


Fig 51 Roentgenogram of an autopsy specimen of the right wrist joint, and photomicrograph through the radiocarpal and radio-ulnar joints showing replacement of cartilage by fibrous tissue and atrophy of bony trabeculae Only the tip of the absorbed ulna is shown in this section, and it is surrounded by dense connective tissue

illustrates the destructive changes in the ulna of a patient with advanced rheumatoid arthritis who did not have the opera-glass hand syndrome In tissue sections obtained at autopsy from this latter case the styloid process and ulnar head were replaced by dense acellular fibrous tissue in which inflammatory changes were either absent or, when present, were of minimal degree (Fig. 51).

Identical roentgenologic changes in the ulnocarpal articulation were present in a patient having psoriatic arthropathy reported by Shlionsky and Blake[5] Thus, it is evident that the loss of osseous structure of the ulna at the wrist joint is not limited to patients with the opera-glass hand syndrome

Absorption of the head of the femur resulting in a deformity of the unilateral protrusio acetabuli type ("Otto pelvis") was present in one of the patients (Case IV) of this report Among the nine previously reported cases of the opera-glass hand syndrome, only one had destructive changes in the hip joints.

Destruction of bone of which the articulations are composed, and the resulting deformities which have been presented in this report, are not restricted to the skeletal parts of the hands A number of terms have been

applied to the condition or variety of conditions in which marked absorption of bones adjacent to and forming joints occurs generally throughout the body. Considerable confusion now exists as a result of this reduplication of names. Stursberg[3] in 1935 reported two cases suffering from polyarthritis and exhibiting destruction of joints, in one the joint changes were confined to the feet He introduced the term "polyarthritis mutilans" This term was discarded by Schuller[9] who, on the basis of the histologic studies by Reinhard,[10] pointed out that not only is the joint but also the epiphysis and diaphysis involved and preferred the term "osteoarthropathia mutilans." It is *also probable that the cases described by Blum*[11] *as "osteoarthropathia* microatrophicans" belong to this same group. In a recent report by Crain,[5] the term "generalized absorptive arthritis" was recommended. It is evident from a survey of these reports that the various entities described under a number of names represent a closely allied fundamental pathologic process It is not unreasonable to suspect that the cases of so-called psoriatic polyarthritis with extensive joint mutilation should be included in this same *category According to Brailsford*[12] *similar changes may occur in such* apparently unrelated diseases as thrombo-angiitis obliterans, hematoporphyrinuria and scleroderma. The exact pathogenic relationship between these conditions occurring in patients with polyarthritis must await further investigation.

From an analysis of the published cases of the opera-glass hand and of the four cases of this syndrome being reported it is evident that the deformity is usually associated with the marked bone absorption of advanced rheumatoid arthritis. In the previously reported nine cases the average duration of the disease was twenty-four years; in these four additional cases the average was twenty-three *years The frequent occurrence of ex*tensive bone absorption involving joints of the body other than the hands in patients with long standing rheumatoid arthritis adds emphasis to the

porosis in the bone adjacent to the joint. It is well known clinically that as rheumatoid arthritis advances the pain on passive manipulation gradually diminishes and finally practically disappears The loss of sensitivity to pain renders these joints subject to trauma It is probable that trauma represents an important accessory factor in the production of subluxation and the deformities which result in hypermobility.

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SPA THERAPY FOR PATIENTS WITH ARTHRITI AND RELATED DISORDERS*

WALTER S. MCCLELLAN

For many centuries patients with rheumatic conditions have visited sp and health resorts where mineral waters, muds and other natural agent are available, to obtain treatment There are many favorable reports regarding the beneficial results of spa treatment

Many physicians had believed that the mineral waters and peloids have an important role in the total regime available at well controlled spas and health resorts and that, with proper supervision, they contribute directly to the beneficial results which many patients with arthritis and related disorders obtain from spa therapy Other physicians give no credit to these natural agents and state that any improvement is psychologic and due entirely to the regulated regimen

Baudisch[1] has reviewed progress in the study of natural healing waters and has pointed out that the information obtained from newer chemical analyses, studies of radioactivity and spectrum analysis, now provides a rational explanation for the empiric observations of the past centuries The specific importance of minerals in enzyme systems and hormone secretions has been reviewed by the same author [2] The importance of the skin absorption of gases from mineral waters has been studied recently by the author and his coworkers,[3, 4] who have reported their observations on the absorption of carbon dioxide and of radon These studies indicate that bathing in mineral water of various types can produce swings in the balance between the sympathetic and parasympathetic divisions of the autonomic nervous system. Most recently Hench and his coworkers† have reported a remarkably beneficial response of patients with rheumatoid arthritis who received the adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone The importance of this finding and the study of a possible relationship between spa therapy and adrenal cortical function will require further investigation

In the ten-year period from 1932 to 1942, approximately 30,000 patients with rheumatic conditions received treatment at The Saratoga Spa * T patients were under the supervision of many different physicians and it not possible to assemble complete clinical surveys of this entire group

CLINICAL MATERIAL

The data presented in this report are based on the clinical review of th records of 993 patients with some form of arthritis or related disorder, wh were treated in the United States Veterans Hospital at Saratoga Springs, New York, between February 1943 and June 1947 An analysis sheet was prepared for each admission and this was used for the tabulation of summaries presented The total number of patients treated in this unit during

* From the Medical Department of The Saratoga Spa, Saratoga Springs, New York (Published with permission of Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author)

† See p 131

that period was 1280, who had 1481 admissions. Approximately 80 per cent of the patients admitted to this Hospital came for some type of rheumatic condition The Hospital was used for a pilot study to evaluate the influence of the mineral waters and other physical agents in the treatment of veterans with these disorders

The patients all received general hospital care under the supervision of the regular staff physicians of the Hospital The special program of treatment included the use of the naturally carbonated mineral waters of the Saratoga Spa, in the form of baths and packs In addition, electric cabinets, whirlpool treatments, diathermy, radiant energy, massage and exercise were all utilized in the treatment The patients remained in the hospital for a period of one to three months The evaluation of the results of their treatment was made by the staff physicians at the time of discharge The discharge note summarized the changes which had occurred in the physical condition of the patient, with an estimation of their response to treatment The results of treatment were graded as marked, moderate or *slight improvement, unimproved, deceased,* or transferred

Table 36 Age Distribution of All Patients Treated

AGE GROUP	NUMBER	PER CENT
Under 20	55	4 2
21–30	174	12 9
31–40	195	15 3
41–50	301	24 5
51–60	475	37 2
61–70	58	4 5
71–80	19	1 3
Above 80	3	0 2
TOTAL PATIENTS	1,280	100 0

Age Distribution Nearly all the patients had served in either World War I or World War II A few were veterans of the Spanish-American War and a few had served only in the peacetime army. Table 36 shows the age distribution of the patients treated in the hospital This table has been prepared for the entire group of 1280 patients, but it represents a fair spread

fourth decades This latter group were for the most part veterans who had *served in World War II, while those in the fifth and sixth decades were* mainly veterans of World War I

Duration of Illness The data included in Table 37 also cover the entire group of patients It is likely that those with rheumatic disease would show a slightly higher proportion with symptoms beyond one year because a considerable number of the nonrheumatic patients were admitted for some acute condition Approximately three-quarters of the patients admitted to the Hospital had presented symptoms for one or more years and nearly half of these patients in excess of three years. The patients admitted for treatment of their rheumatic conditions were mainly in the chronic group In fact, some were in the advanced chronic group and were entirely and

completely bedridden, and some were unable to walk and could get about only in a wheel chair.

Types of Rheumatic Conditions In the further analyses of the data presented all figures will refer directly to the 993 patients who were admitted for some form of arthritis Table 38 shows the distribution of all the patients

Table 37. Duration of Illness

DURATION	NUMBER	PER CENT
Under 1 year	362	28 5
1 and 2 years	341	26 4
3–5 years	208	16 2
6–10 years	133	11 2
11–15 years	56	4 3
16–20 years	23	1 0
Over 20 years	86	6 8
Unknown	71	5 6
TOTAL PATIENTS	1,280	100 0

in this group on the basis of the usual classification of rheumatic diseases The largest group was diagnosed as osteoarthritis in its various forms and included 438 of the patients treated Rheumatoid arthritis was second on the list with a total of 331 patients, nearly all of whom were classified as chronic The remainder of the patients represented smaller groups as indicated in the table From the study of this table it is clear that the two large groups of osteoarthritis and rheumatoid arthritis accounted for a large majority of the patients

Table 38 Types of Arthritis Treated

DIAGNOSIS	NUMBER	PER CENT
Osteoarthritis	438	44 1
Rheumatoid arthritis	331	33 3
Traumatic arthritis	94	9 5
Mixed, rheumatoid and osteoarthritis	41	4 1
Rheumatoid spondylitis	36	3 6
Specific infectious (G C and T B)	31	3 1
Gout	15	1 5
Unknown	7	0 8
TOTAL	993	100 0

RESULTS OF TREATMENT

The results of treatment recorded by the Hospital physicians on discharge have been tabulated for each of the groups of rheumatic disease in Table 39 They show that 262 patients (26 3 per cent) were slightly improved, 568 patients (57 2 per cent) were moderately improved and 86 patients (8 7 per cent) were markedly improved Thus gives a total improvement per cent of 92 2 Only 77 patients (7 8 per cent) were unimproved or were transferred for other treatment No deaths occurred in the series

It is obvious immediately that any statistical analysis dealing with the number of patients treated in groups three to eight would have little value. Because of the larger number of patients with osteoarthritis and rheumatoid arthritis, a more detailed study was made

Osteoarthritis. In Table 40 are presented the results of treatment for patients with osteoarthritis, analyzed in relation to the total amount of

Table 39 Results of Treatment

TYPE OF ARTHRITIS	NUMBER	SLIGHT IMPROVEMENT	PER CENT	MODERATE IMPROVEMENT	PER CENT	MARKED IMPROVEMENT	PER CENT	UNIMPROVED	PER CENT
Osteoarthritis	438	101	23.4	260	59.3	38	8.6	39	8.7
Rheumatoid arthritis	331	81	24.5	213	64.3	17	5.1	20	6.1
Traumatic arthritis	94	38	40.4	31	33.0	19	20.2	6	6.4
Mixed (rheum. & osteo)	41	12	29.0	21	51.2	4	9.9	4	9.9
Rheumatoid spondylitis	36	10	27.8	20	55.6	4	11.1	2	5.5
Specific infectious (G.C., T.B., etc)	31	10	32.3	17	54.8	1	3.2	3	9.7
Gout	15	7	46.7	4	26.6	3	20.0	1	6.7
Unknown	7	3	42.8	2	28.6	0	0.0	2	28.6
ALL TYPES	993	262	26.3	568	57.2	86	8.7	77	7.8

treatment received. The total amount of treatment was gaged by the number of mineral water baths, because for practically all patients it represented the major feature of the program Even with ten baths or less, some patients showed improvement, but the proportion of those who were not improved was much higher than in the other groups When the patients received from eleven to twenty-one baths, there was some increase in the

Table 40 Results of Treatment of 438 Patients with Osteoarthritis

BATHS	SLIGHT IMPROVEMENT	PER CENT	MODERATE IMPROVEMENT	PER CENT	MARKED IMPROVEMENT	PER CENT	UNIMPROVED	PER CENT
1–10	4	12.5	16	50.0	4	12.5	8	25.0
11–21	35	27.2	65	52.4	12	10.2	12	10.2
22–42	48	20.6	149	63.7	19	8.1	17	7.6
Over 42	14	28.5	30	61.2	3	6.1	2	4.2
TOTAL*	101	23.4	260	59.3	38	8.6	39	8.7

* Total per cent of improvement, 91.3%

percentage of patients who obtained benefit. When the baths were continued longer, over twenty-one in number, there was considerable increase in those who showed moderate improvement. When the treatment program extended beyond what usually is considered two average courses of [illegible] benefit was evident The patients who remained [illegible] ourse of treatment were more seriously [illegible] roups

Summation of the results of treatment for all the patients in this group shows that approximately one-quarter were rated under slight improvement, 60 per cent moderate improvement and nearly 9 per cent marked improvement, making a total over-all improvement figure of slightly over 90 per cent Approximately 9 per cent were discharged, either as unimproved, or transferred to another hospital

Rheumatoid Arthritis In surveying the results of treatment in this group (Table 41) with reference to the total amount of treatment, it is evident that those who received less than ten baths apparently received no special benefit. A few were reported as showing slight improvement In the second and third groups, namely, those who received from eleven to twenty-one

Table 41 Results of Treatment of 331 Patients with Rheumatoid Arthritis

BATHS	SLIGHT IMPROVEMENT	PER CENT	MODERATE IMPROVEMENT	PER CENT	MARKED IMPROVEMENT	PER CENT	UNIMPROVED	PER CENT
1-10	8	44 6	3	16 6	0	0 0	7	38 6
11-21	22	27 9	53	63 4	3	3 8	4	4 9
22-42	40	23 0	117	67 3	14	8 1	3	1 6
Over 42	11	19 3	40	70 2	0	0 0	6	10 5
TOTAL*	81	24 5	213	64 3	17	5 1	20	6 1

* Total per cent of improvement, 93 9%

or from twenty-two to forty-two baths, there was a considerable decrease in the percentage of those who were discharged as unimproved However, percentage figures for the small group are not significant It is also clear that the percentage of those discharged with marked improvement increased, particularly among those receiving the second series of bath treatments. The figures reported for those receiving more than forty-two baths are not significant because of the small number of patients It should also be noted that those receiving the longer series of baths were also the most [illegible] eriod of hospitalization [illegible] ɔined, it is evident that [illegible] improved, one-quarter slightly improved, and approximately 5 per cent markedly improved, showing an over-all improvement figure of nearly 94 per cent

COMMENT

In dealing with a disease like arthritis which shows many different manifestations and which, because of its chronicity, has persisted in many patients over a period of years, one cannot be dogmatic in saying that this or that form of treatment has brought about the results noted However, [illegible]

will many times be changed into a most cooperative person when he finds some relief for the pains which trouble him when he moves about The undernourished frequently show appreciable gains in weight.

The baths and other forms of physical treatment have been recognized as important therapeutic agents for patients with rheumatic disease This is

especially true for patients with osteoarthritis. In treating patients with rheumatoid arthritis, a more varied therapeutic program generally is used.

In analyzing the manner in which spa treatment can play a part in influencing the disease process of arthritis, it seems that when used with regularity, it can definitely influence certain of the precipitating, possibly even the initiating, factors in rheumatoid arthritis. In making this statement it is the belief of the author that spa treatment, no matter what type of water is used, is definitely a constitutional form of treatment. It influences the host through physical and chemical changes of cells and organs so that the host may resist the invasion or the extension of the disease process True, it is difficult to prove this point of view objectively. However, it is well known that definite improvement in these patients may result from the use of mineral waters or peloids which vary widely in their constituents.

When the disease process is more or less well developed, there is pain, stiffness, spasm and swelling of the affected joints The program of treatment utilizing mineral waters and muds usually will relieve pain, decrease spasm, increase motion and decrease swelling These factors, then, which represent pathologic physiology of these disease processes, do show definite change *when the patients are treated at the spa or health resort They are evidence* that some change for the better has occurred The way in which mineral waters produce these effects must have further study before it can definitely be stated that any specific chemical or agent in the water is responsible for any particular response in pathologic physiology.

In many of the patients with rheumatic diseases, and particularly in the group which is the basis for this presentation, chronic changes such as atrophy of muscles, deformity, persistent exudate, and in fact ankylosis, are common findings With the treatment program which these patients received, it was possible even in those patients with more advanced disease processes to note improvement with the increased range of motion and with proper therapeutic exercise programs for improvement in the strength of the muscles involved The time spent in the "cure" program here was not sufficient to obtain the maximum restoration of improvement of these more severe chronic cases In fact, they represent mainly those patients who were treated for the longer periods because of the severity and chronicity of their conditions

The program built around mineral waters and associated treatments, particularly when occupational therapy and corrective exercise are included can be of real benefit in the rehabilitation of many patients with arthritis It must be remembered that an adequate program of rehabilitation for these patients is more difficult than for the patient with static disability such as the loss of an extremity, the loss of an eye, or fixed paralysis, which does not change from year to year The patient with arthritis may progress, making it more difficult to plan a long range program of rehabilitation It is possible for the spa, with its periodic therapeutic program, to be of value in this phase of care for the patient with rheumatic disease

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4 —— and Comstock, C R, Jr Arch Phys Med, *30* 29, 1949
5 —— *Ann Int Med, 18 825, 1943*

REHABILITATION IN RHEUMATOID ARTHRITIS*

K. G. HANSSON AND JACK LOVELOCK

When we review the management of the patient with rheumatoid arthritis during the last few decades, we find many different approaches. We have tried spa therapy, various diets, removal of foci, vaccine therapy and chemotherapy. In spite of all our efforts there is doubt that we have influenced or diminished that large group of our fellow men who eke out their existence on crutches, in wheel chairs or in bed because of rheumatoid arthritis. We all know of patients who have had the best possible care and, in spite of this, have progressed to severe joint deformity, muscle atrophy and general disability. We find patients who have suffered an attack of rheumatoid arthritis with a variation of residual scars. They may have badly deformed hands, an ankylosed hip or knee, a painful, stiff back or general muscle atrophy. All these symptoms and signs are often found in the same individual. To add to this discouraging picture we must admit that the disease is usually progressive. Over the period of many years we stand by while the patient takes to canes and crutches. When locomotion becomes impossible the patient must resort to the wheel chair and finally, in the progressive cases, lose all freedom and become bedridden. These patients constitute a real challenge to the medical profession in general and to the rheumatologist in particular. What, then, do we have to offer our convalescent patient with rheumatoid arthritis, both early in his illness and later in his deformity?

In spite of the recent reports of Hench, Kendall and their coworkers† of the effect of cortisone in rheumatoid arthritis, the probable paucity of supplies for many years together with the present expense will limit its use in the prevention of disability and deformities and it cannot correct those already structurally established. No one will pretend that our present treatment of the disease is satisfactory, and there was until very recently much to be said for the view expressed by Stecher[1] that "since there is no clear concept of the etiology of the disease, therapeutic ineffectiveness is almost guaranteed." In practice we cannot afford to adopt this depressing attitude in dealing with patients, and we must use the utmost at our disposal. Physical measures have been well tried and are of proven benefit, in many places they are still the backbone of symptomatic treatment, but it is the deformity reduction that we must aim at as well as this relief.

THE SCOPE OF REHABILITATION

Though by definition "rehabilitation" really implies treatment from the onset until the return to remunerative employment, in accepted medical practice it is spoken of as help after the definitive treatment has ended. Rehabilitation has recently been very well reviewed by Rusk[2] who stresses it as "the third phase of medical care." It implies the long time treatment of the chronic case in the convalescent stage, with particular emphasis in rheumatoid arthritis specifically on the amelioration of deformities as well as on the relief of symptoms. This naturally is the province of no particular

* From the Hospital for Special Surgery, New York, N. Y.
† See p. 131

especially true for patients with osteoarthritis In treating patients with rheumatoid arthritis, a more varied therapeutic program generally is used

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THE SCOPE OF REHABILITATION

Though by definition "rehabilitation" really implies treatment from the onset until the return to remunerative employment, in accepted medical practice it is spoken of as help after the definitive treatment has ended Rehabilitation has recently been very well reviewed by Rusk[2] who stresses it as "the third phase of medical care" It implies the long time treatment of the chronic case in the convalescent stage, with particular emphasis in rheumatoid arthritis specifically on the amelioration of deformities as well as on the relief of symptoms This naturally is the province of no particular

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specialty, but it is agreed by all that physical methods play a large part. It is this aspect that we wish to discuss, fitted into the general over-all background of medical, surgical, radiologic, social and other treatments The appropriateness of any measure depends on the pathologic activity or quiescence at the moment, as well as on the reaction of the individual, so that critical knowledge and wide experience are needed for accurate prescription. This applies to physical no less than to other measures.

Rheumatoid arthritis is so protean in its manifestations that the treatment of chronic cases as well as of all others must be carefully individualized. However, here we will be forced by space to make generalizations, a dangerous thing, realizing that some are not always strictly applicable. The scope of rehabilitation starting really from the beginning of the onset of disease has been stressed recently in poliomyelitis by Hansson[3]

Firstly, we must utilize all measures for deformity prevention or at least insure that if joint ankylosis does supervene it is in the best position for that particular patient. Secondly, thanks to the dynamic approach to convalescence by the Army Medical Corps during the last war we have a more (admittedly guardedly) optimistic attitude with more therapeutic modalities to offer our convalescent patient. This is one of the few benefits of our last World War The approach proved eminently successful in the armed services and it is our duty to provide our civilian convalescent patients with the same complete after-care that we offered our soldiers during the war Thirdly, we must treat our patients as individuals with different mental and physical reactions to all our treatments, psychologic, pharmacologic, radiologic or physiologic

It is difficult to fit any treatment of a disease of unknown etiology into neat headings, but for the sake of clarity we will try to systematize the physical aspect somewhat artificially under the five headings. Body Mechanics, including position, rest and exercise, Passive Physical Therapy, including heat and massage for symptomatic relief, Therapeutic Pool, Ambulation, in its various grades, and Occupational Therapy and Gadget Board

BODY MECHANICS, INCLUDING POSITION, REST AND EXERCISE

Many patients are forced to remain in bed over long periods of time, so rest must be stressed equally with activity, general for the whole body and local for the affected joints Supervised bed rest and removal of weight-bearing strains is one of the most important things in deformity prevention This is well emphasized by Margolis[4] and might receive more attention than it does at present Deformities should not be allowed to develop, yet a patient with chronic rheumatoid arthritis who has just had the benefit of supervised management in treatment may present the following aspect·

1 [illegible] is increased

This [illegible] is also

due t[illegible] he use

of eyes, which will tend to bend the head and neck forward Amelioration can be aided by the removal of head pillows We also recommend periscope glasses which permit the patient to read a book held on the chest without raising the head.

2. The shoulders show cupping in front and round shoulders posteriorly The chest is usually depressed and vital capacity is low. This type of deformity is also predisposed to by supports under the neck and shoulders.

Maintaining the position of the shoulders in flexion lead
of the pectoral muscles To prevent this deformity we m
under head and shoulders and instead place a small pill
shoulder blades. Breathing exercises of both thoracic and
type should be used twice a day

3 With the increasing dorsal curve that goes with roun
nentioned above, the patient may develop a compensato
ngle or a flat back with poker spine This lumbosacral angl
y the abdominal muscles in front and by the gluteus maxim
he pelvic roll type of exercise is therefore indicated to prev
mbosacral angles and to assist continued freedom of mov
mbar spine.

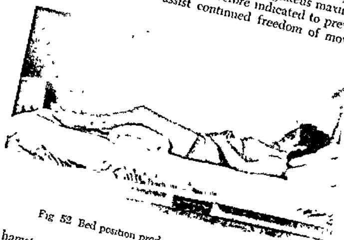


Fig 52 Bed position producing common deformities

4 The hamstring muscles may be in spasm, increasing flexion contr
and backward subluxation of tibia on femur They become tight an
shorten due to the flexion of the knees To prevent this, no support s
be permitted under the knees and the hamstring muscles should be stre
out to their full length daily This is supplemented by quadriceps se
exercises. By maintaining the tone in the quadriceps and the full leng
the hamstrings we may prevent certain types of flexion contractures in
knees.

5 When the feet are neglected during long bed rest they may sho
tendency to weaken in dorsal flexion and inversion The result is pronat
of the foot with more or less drop foot It is therefore recommended t
the bed be supplied with a foot board against which the patient can pl
the feet and thus maintain proprioceptive reflexes

Position Normally the position in bed is that most conducive to cor
fort. Figure 52 shows a patient with rheumatoid arthritis in the positio
of greatest comfort, with the affected joints well supported to relax th
painful spasm in neck, hip and knee flexors and with hands on the abdome
for relaxation of the upper extremities, and for warmth and comfort of the
peripheral members with their frequent circulatory deficiency It is also
the position most conducive to the common flexion and adduction deformi-
ties, with the drooping and fixation of the ribs in expiration and the dropped,
unsupported feet made worse by the weight of the bed clothes.

The same patient is shown in Figure 53 in a much less comfortable and admittedly relatively strained position While we agree with Hartung[5] that "it is important in these days not to revive the mechanical school of physiology of Goldthwaite"[6] we also agree that chronic rheumatoid arthritis is a constitutional disease and until its etiology is clear the most effective treatment is directed toward the various constitutional derangements. So we do believe that where splinting, slings and other mechanical means of ensuring local rest in a position of extension are not indicated, some useful purpose may be served by the adoption for short periods, under trained supervision, of such rest positions as shown. Note the bed board under the mattress preventing sagging of the springs, and the foot board with the slight gap for the heels The weight of the bed clothes is taken from the feet by the board and from affected knees, hips and lower trunk by the metal

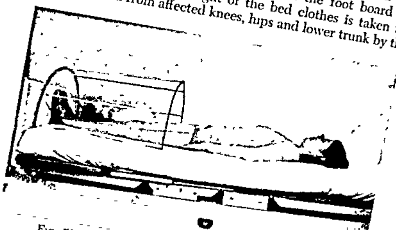


Fig 53 Correct supine position to prevent deformities

cradle over the lower extremities No head pillow is allowed but the use of periscope glasses permits reading without neck flexion. A mechanical book support is easily arranged over the chest or abdomen, but here it is purposely not shown Instead (cf Fig 52) note the expanded chest and backward shoulders helped by a small interscapular pillow, not visible here

Quite apart from the adoption for short periods of this strained position, however, much harm might be prevented by the use of such simple mechanical aids as mentioned, for we must agree that for the long term incapacitated person such aids to mental relaxation as reading are an obvious necessity This must be encouraged in such a way as to avoid production of deformity, and one simple physical method is exemplified.

Changes of position are both desirable for the patient and necessary for the treatment One such positional change is to prone lying (Fig. 54) still in general extension and aided by a knee pillow and foot gap The practical adoption of the positions suggested obviously depends on the state of activity of the disease. That must be a matter for the individual physician to decide on from his knowledge and experience, but it is suggested that short regular periods throughout the day should be tried, always under sympathetic trained supervision

Rest and Exercise A similar decision must be made on the balance to

be struck between rest and activity We now know the changes in metabolism that occur during inactivity We know the loss of calcium and phosphorus as well as the increase in nitrogen excretion and other changes in our body chemistry, as shown recently by Deitrick and his coworkers,[7, 8] in normal men In normal health, balance is always difficult to arrive at, as pointed out long ago by Hilton[9] and recently stressed by Lovelock[10] In pathologic states it is even more difficult, depending on the psychologic and physiologic reaction of the individual and on the physician's conception of the disease

However, complete bed rest should always be relieved, particularly in the absence of objective evidence of acute inflammation, by definite bed exercises Such patients should be encouraged to change their positions and assume such postures as supine and prone lying, and to turn on the

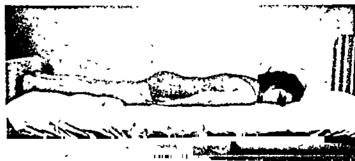


Fig 54 Prone lying in extension to prevent deformities

right side and on the left side Further activity may take many forms varying from once-daily passive movements to reduce the likelihood of ankylosis of involved joints immobilized in split plasters or in extension slings and static muscle contractions to reduce disuse atrophy, through active-assisted to active-resisted movements in the convalescent stages The simplest, most efficient and most practical bed exercise in the relatively quiescent state and in the absence of adequate trained supervision is by means of a stout cane, so widely used during the war for ward drill of men confined to bed by injuries Though the ways of using this are almost unlimited, exercises of extension and abduction should be stressed here just as they are when movements are done under supervision They are older phylogenetically and ontogenetically, and are therefore lost earlier With such a cane we can maintain the grip of the hands, supination and pronation of the forearm, and flexion and extension of the wrist, elbow and shoulder By hooking the handle of the cane under the foot, flexion and extension can be performed at ankle knee and hip If the handle of the cane is hooked over the foot of the bed the patient has a great help in coming to position and also an aid in side flexion and twisting of the spine

Properly timed chosen and performed exercises benefit general body metabolism as well as local joint function In the program should be included breathing exercises and abdominal, gluteal and quadriceps contrac-

tions, while sponge rubber balls are used for strengthening hand movements Whatever exercises are done, however, it should be stressed that little and often is the ideal Occasionally patients and their advisers think that exercise means movements of large range and heavy type, performed relatively infrequently, these are more likely to reactivate quiescent inflammation

PASSIVE PHYSICAL THERAPY, HEAT, MASSAGE AND MOVEMENT

Physical therapy has been used empirically in all forms of arthritis for centuries. While other treatments have changed we still rely to a great extent on heat, massage and movement in the general management of rheumatoid arthritis To these older, simpler treatments, we might add more modern applications by physical means, such as light and electricity in its various forms Physical therapy has developed greatly as a result of the last two World Wars, and we have come to consider the various modalities with more specificity. At the present time we should try to prescribe a certain specific measure for a special symptom found in the arthritis patient

The skeletal system of bones and joints is always involved in rheumatoid arthritis. There are stiffness and swelling of the joints, as well as more or less deformity and the faulty body mechanics already mentioned For stiffness we may use heat, massage and movement, for painful swelling we may apply cold, while various forms of movement and manipulation may be used for the deformity, with postural correction for faulty body mechanics.

The voluntary muscular system with its contained and attached tissue is necessary for static support, and for dynamic functional movement of the whole body. It often shows signs of atony and atrophy, it often gives symptoms of myositis and fibrositis For atony we may use alternating heat and cold and muscle reeducation, for atrophy we may use electrical stimulation, muscle reeducation, muscle setting exercises and maximum-effort or resisted exercises. For myositis and fibrositis, heat of varying penetration and massage, light to deep, are indicated

The circulatory system may show secondary anemia, deficiency of the capillary circulation and congestion of the dependent parts. Then we rely on ultraviolet radiation, hydrotherapy, paraffin baths, iontophoresis and movement.

The respiratory system may show decreased efficiency associated with the drooping and fixation of the chest, when the posterior articulations of the ribs are involved, interference with expansion occurs (Fig 52) Treatment of this has already been mentioned under the preventive aspect

The digestive system largely controls nutrition and includes the gastrointestinal tract and its functions, embracing ingestion, digestion and excretion, including skin elimination. Dysfunction may show as abnormal variations in weight, with poor appetite and constipation, sometimes associated with visceroptosis For these we have ultraviolet radiation as a tonic, hydrotherapy for elimination, massage and exercises including postural exercises for constipation

In the nervous system we have to deal with the peripheral nerves and their control over the voluntary muscles as well as the action of the autonomic system on the various viscera Symptoms may take the form of arthralgia, neuritis and general inability to coordinate. Deep heat should

be prescribed for arthralgia, superficial heat for neuritis, while specific neuromuscular movements encourage coordination

Mental symptoms of a neurotic degree may arise in connection with any of the physical systems. Depression and anxiety are common. All forms of physical treatment can be used as psychotherapy Ultraviolet radiation may have either a sedative or a stimulating effect while occupational therapy plays an important part in maintaining the emotional balance, satisfying the intellectual urge, and occupying the body as well as the mind

THE THERAPEUTIC POOL

This form of treatment combines three of the oldest forms of therapeutics in heat, water and exercise Heat has always been used for its sedative effect in the body In using water in the pool we make use of Archimedes' principle that a body submerged in water will lose as much weight as the weight of the displaced water Warm water enables movements to be made either passively with a minimum of painful spasm or

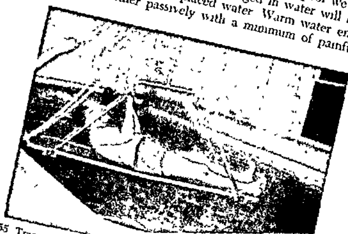


Fig 55 Transport of deformed and ankylosed patient into therapeutic pool

actively with a maximum of enjoyment The movement in the pool consists of local mobilization, passive, assisted or active, for the trunk and extremities, and applied exercise such as walking and swimming Although it is true that some benefit can be obtained by using an ordinary tub bath or tank, they cannot be compared to a therapeutic pool for usefulness or enjoyment.

Transport of an immobilized deformed patient into the pool presents real but not insuperable difficulty It has been found most convenient to build the pool from the floor up to the height of the hospital stretcher (Fig 55) This facilitates the entrance and the exit of the crippled patient However, where extensive ankylosis exists and disease activity forbids weight-bearing, a hoist is attached to the metal stretcher top and raised by chain pulleys to swing the recumbent patient into the water to be received by the physiotherapist

A convenient size for the therapeutic pool is 26 feet by 12 feet with the depth varying from 4 feet to 2 feet Various ramps and underwater seats

facilitate the handling of the patients· Heating, filtration and sterilization of the water are best carried out in a special room. The purity of the water should be tested at the beginning and at the end of each day Bacteriologic tests should be made once a week A solarium especially for winter use is an important adjunct to the therapeutic pool. After twenty years of experience in treating patients with rheumatoid arthritis, we feel it is safe to say that there is no treatment the patient will enjoy so much as the time spent in the therapeutic pool Many patients begin to take a new interest in life, and if this new interest can be transformed into beneficial activity, half the benefit of treatment is gained.

We have mentioned applied exercise, particularly the essential one of walking In the patient illustrated on the hoist (Fig. 55), the neck and shoulders are ankylosed in flexion This naturally adds balance difficulties

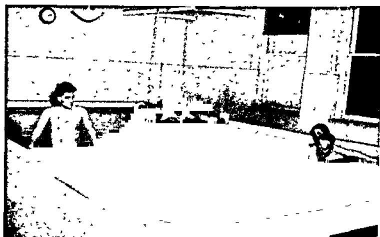


Fig 56 Therapeutic pool for early activities

[illegible] eneral walk- [illegible] ion to his body weight being largely taken by the water, he is aided by one inflated rubber ring These early attempts at walking are best started in the pool, where the legs can be moved first without weight-bearing, later a graded amount of weight can be allowed depending on the depth of the water and the number of rubber rings used, as seen in the left side of the same picture (Fig 56) Also, nothing can give the same confidence as the fluid support of warm water.

Once again, however, we must stress the importance of keeping pool movement, passive or active, specific or applied, within the requirements of the pathologic state of the moment Chronic quiescent cases in which deformities are largely due to periarticular contractures benefit greatly from gentle forced movements, or prolonged forced extension with web strapping on metal splints under the warm water.

AMBULATION

This is a severe problem, especially in patients with involvement of the weight-bearing joints of the lower limbs For many years we have advised

rest for all arthritic joints of different etiologies Over the last twenty-five years it has become evident that rest and immobilization have had very depressing results. Therefore it seems rational to attempt earlier ambulation This is especially important when the disease has been arrested or has burned itself out The following points might be considered.

1. If the upper extremities are quiescent and the lower extremities badly involved, pre-crutch walking exercises should consist of movements that will strengthen the grip, the triceps and muscles supporting the scapula A typical exercise is the pushup with the patient sitting in bed and carrying



Fig 57 Early ambulation in walker

the body weight on the hands Such exercises are facilitated by a Balka frame on the bed from which a trapeze or other apparatus can be suspended

2 As already mentioned the first ambulatory attempts by a patient badly crippled by rheumatoid arthritis are safest performed in the therapeutic pool Progress after that consists in transfer to a walker (Fig. 57) In this, balance is the first physiologic consideration confidence the even more important primary psychologic one The patient should be allowed first to get used to weight-bearing on the feet and should then be taught balance by swinging rhythmically in all directions This restores the afferent proprioceptive and exteroceptive stimuli from the lower limb and the impulses from the vestibular apparatus, neck or eyes,[11] with their coordination in the cerebellum before relay for integration to the higher centers and subsequent transfer into afferent stimuli resulting in appropriate coordinated muscle action The patient shall be taught to push down on his hands and, where possible, also to lift the legs from the floor This requires fully

trained supervision, and in practice all too often the limitation of movement imposed by the disease prevents anything more than the merest shuffling gait However, even if it be not the ideal, that allows a greater degree of physical freedom.

3 When the patient has mastered the walker he should be measured for crutches, and the greatest precision should be used to obtain the proper length The patient is first placed on crutches with his back toward a wall. He should again experience weight-bearing and balance, lifting the crutches alternately from the floor, placing a crutch forward and return, and later one foot forward and return. When the patient is ready after these preliminaries to start actual walking with the crutches he should be aided in picking the gait that seems best suited to him There are four gaits: (*a*) the four point gait where the left crutch is placed forward followed by the right foot, then the right crutch forward followed by the left foot; this is a slow gait but offers great stability and safety; (*b*) the two point gait where the left crutch and right foot come forward at the same time, followed by the right crutch and left foot, (*c*) the three point gait where both crutches and one foot are placed forward at the same time and are then followed by the other foot; and (*d*) the swing-through gait where both crutches are advanced at the same time, followed by both legs swinging through to complete the step This is the speediest method of ambulation but has no other advantages In practice, where a variable degree of fixation of the lower joints frequently exists, a shuffling gait precedes a well coordinated stepping gait, and more weight-bearing in the axilla than is theoretically desirable often has to be permitted owing to involvement of the upper extremities, especially weakness and deformity of the hands However, it suffices to prevent the patient's being bound to the bed or the wheel chair, and allows short-time freedom for essential needs In practice a frank attitude depending on functional possibilities has to be adopted rather than an idealistic conception

4. Walking and gait training are aided considerably by gymnasium work, especially walking between parallel bars with mirrors placed at both ends so that the patient can correct himself in technic, prevent poor walking habits and learn the proper length of the step.

5. As soon as the patient has learned some form of ambulation it becomes important to learn how to get into a regular chair or wheel chair, and how to get out of such a chair This should preferably have arms that the patient can grasp, after which he turns his body and slides into the seat The opposite technic is used in getting out of the chair. This performance often requires much persistent training that is of great value in the independent life.

6. The ambulatory patient walking with crutches, or later when progress has been made to canes, is much disturbed by steps or ramps. If a hand rail is available as a fixed point only one crutch is used and the patient can usually hoist his body up the step If no hand rail is present, the patient can raise the right crutch to the first stair; raise the right foot, turning the body to the left crutch, straighten the right knee and push down on the left crutch, the patient will then be able to raise the left leg to the step This training in stair climbing is tedious, but when mastered will help enormously toward physical freedom

OCCUPATIONAL THERAPY AND GADGET BOARD

Another name for occupational therapy might be "fun and function" because we distinguish between the diversional and functional aspects The science of medicine aims to develop the latter physiologic side, but the art of medicine prevents our closing our eyes to the emotional psychologic side. The arthritic patient is stimulated by diversional therapy. It [illegible] the apathy which accompanies [illegible] by a therapist with suitable per- [illegible] knowledge However, we are [illegible]



Fig 58 Functional activities in occupational therapy hand loom for upper extremities

discussed under therapeutic exercise and we shall now survey exercises with a purpose If we analyze the kinesiology of the upper extremities we find that the movements are usually coordinated and follow a certain pattern. Flexion of the fingers goes with flexion of the elbow that goes with flexion and adduction of the shoulders Likewise the extension of the fingers, wrists, elbows, and shoulders are closely coordinated The occupational therapy prescribed should, therefore, be based on these reflex patterns, remembering that in rheumatoid arthritis the extension movements more usually suffer in the disease process Hence, extension is again stressed here as it was in specific exercises As a simple example consider the work on a loom (Fig 58) This has the advantage of occupying both upper extremities at the same time The grip of the hand is necessary to hold the beater or the shuttle, and coordinated motions in elbows and shoulders are easy to perform This maintains or improves the function of the joints and strengthens the involved muscles

In a similar way we recognize different reflex patterns in the lower extremities where flexion in the hip and knee are coordinated with dorsal

flexion of the foot, while extension of the hip and knee are coordinated with plantar flexion of the foot These movements are coordinated when the patient is working a bicycle saw (Fig 59). It is evident that different types of occupational therapy can also be used for corrective purposes, while extensors can be strengthened in the presence of flexion contractures and a pronated forearm can be used in supination The foot pedals of a bicycle saw can be altered in order to produce flexion of the lower extremities instead of extension.

Needless to say, such functional activity also benefits the patient's mental outlook, gives him the pleasure and satisfaction of making things, and may even lead to an avocation In this respect much use can be made of such simple activities as typewriting or clay moulding



Fig 59 Occupational therapy bicycle saw for lower extremities

For the crippled rheumatoid arthritis patient it becomes very important to attend to his personal hygiene if this ability has been lost The rehabilitation service at Bellevue Hospital uses a list of ninety-six items to test the patient's capacity for daily living[2] They consist of bed activities, [illegible] undress, hand activi- [illegible] the needed abilities

At the Hospital for Special Surgery we use for some of these a gadget board or instrument panel in retraining, under therapeutic supervision, for the more necessary acts of daily living The board is provided with various gadgets and fixed on the wall in such a way that it can be raised or lowered This is to suit different patients while sitting or standing, and to oblige the patient to use the arm at different shoulder heights

Only the more necessary simple acts are taught, arranged in order of physiologic functional necessity. They entail the ingestion and excretion of food and drink, the clearing of the air passages, and the essential body movements of shifting position and dressing These necessary acts include

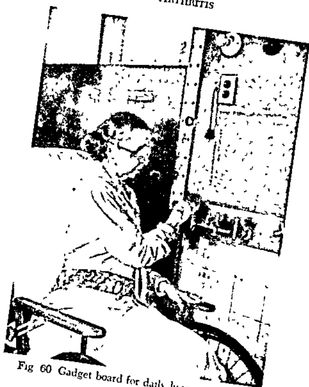


Fig 60 Gadget board for daily living activities

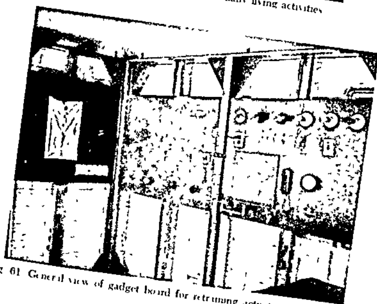


Fig 61 General view of gadget board for retraining activities of daily living

the pressing of a toilet flush lever, the turning of faucets of different types and resistances (Fig. 60), and the screwing of the tops of tooth paste tubes and powder and shaving cream jars.

Scarcely less necessary is the ability to handle a brush used either for the hair or the clothes. A large number of different types of electric light fixtures are also included (Fig. 61). The ability to move around the house requires the opening of various doors of closets and rooms. To train the patient we therefore include door handles, locks, keys and bolts of different sizes and resistances A telephone dial and receiver can be used for practice. Buttons and safety pins of various sizes are available, also matches and many other gadgets. This type of training can be utilized by patients in their leisure hours, without competition pressure but with sympathetic guidance. An advancement in this may be seen at any big rehabilitation center where prevocational and vocational training require increased strength as well as varied neuromuscular coordination The patient with rheumatoid arthritis, however, is always a slight risk in advanced rehabilitation and care must be taken not to precipitate a flare-up of the disease

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AN ELECTROMYOGRAPHIC STUDY OF RHEUMATOID ARTHRITIS*

SEDGWICK MEAD AND MARGARET H. CLARE

The purpose of this investigation was to extend the observations begun by Morrison et al [1] in a pioneer paper on the subject. The specific objective was to determine whether denervation (fibrillation) potentials are present in rheumatoids. Such potentials were not seen in the material of Morrison et al We have observed them in only one case Other abnormalities searched for included *spontaneous electrical activity* of the motor unit type (fasciculation), spasm, contracture and tremor

* From the Division of Physical Medicine, Washington University School of Medicine and the Arthritis Clinic, Washington University Clinics and Allied Hospitals, St Louis, Missouri

MATERIAL AND METHODS

No attempt was made to select patients, the majority of whom were seen in the Arthritis Clinic, on wards, or were kindly referred by private physicians. Seventeen patients with indisputable rheumatoid arthritis were studied* as well as one patient with gonococcal, one with meningococcal, one with degenerative arthritis, one with frozen shoulder (periarthritis) following subacromial bursitis, and one with group or collagen disease (probable lupus erythematosus disseminatus) See Table 42

*Table 42 Seventeen Patients with Rheumatoid Arthritis**

INITIALS	AGE	SEX	DURATION OF DISEASE	JOINTS INVOLVED	ACTIVITY
E B	61	M	6 years?	Knees, shoulders	Inactive
S P.	51	M	10 years	Diffuse, nonspinal	Acute
F. D	49	M	6 months	Hand, wrist, knees	Acute
R H	42	M	10 years	Spine, sacro-iliacs	Subacute
W B	32	M	16 years	Spine, hips shoulder	Acute
V D	27	M	6 years	Spine, hips	Inactive
L R	26	M	15 years	Spine, hips	Inactive
C C	16	M	4 years	Hip, knees	Subacute
E R	44	F	2 years?	Diffuse nonspinal	Inactive
R C	43	F	6 years	Diffuse, nonspinal	Subacute
T W	10	F	12 years	Diffuse, nonspinal	Acute
M C	30	F	6 months	Knees, ankle	Subacute
N W	27	F	15 years	Diffuse, hips	Inactive
V I	27	F	2 years	Knees, ankles, hips	Acute
C G	25	F	15 years	Diffuse	Inactive
E P	23	F	6 months	Diffuse	Acute
M A	14	F	1 year?	Diffuse hips	Acute

* Criteria established by the American Rheumatism Association ¹

Muscles in relation to affected joints were chosen for study Surface electrodes were employed with a three-channel Grass inkwriter oscillograph for preliminary study, supplemented by coaxial needle electrodes with photographic recording from a cathode ray oscilloscope and suitable amplifiers If abnormalities were not noted in the preliminary exploration, the latter method was not routinely used

With each patient an attempt was made to secure maximal relaxation by careful positioning, avoidance of noise and bright lights, and by verbal encouragement Sometimes a second visit to the laboratory succeeded when the first was merely a training period The record was then scanned for evidence of spontaneous activity not attributable to poor relaxation In a few patients pain at rest was severe enough that relaxation was never obtained Active and passive movements were then carried out, sometimes with a 1-kg weight in the hand for loading Passive stretching was used to elicit evidence of spasm or contracture Agonist-antagonist pairs were used in a few patients for study of tremor patterns

* Three patients were studied at the Massachusetts General Hospital, Boston, through the kindness of Dr Walter Bauer, the Arthritis Clinic, and Dr Robert S Schwab, the Brain Wave Laboratory

symptoms in nearby joints. Positive findings have likewise occurred in comfortable patients with old, burned-out disease. Six of the seventeen patients showed no electromyographic abnormalities.

We did not search for evidence of spasticity (lesion of corticospinal tracts). Spasm we considered to be present when muscles previously at rest and electrically silent showed protective contractions accompanied by pain during passive stretching. This is a difficult finding to interpret since a patient not sufficiently trained may unconsciously activate both the assisting and the stretched muscle as a result of apprehension or in trying to assist the movement. We felt that spasm was unequivocally demonstrated only in patient W B Contracture was said to be present when a muscle could not be stretched its normal length in spite of electrical silence. Spontaneous resting activity of the motor unit type occurred as random spikes or occasionally as a unit repeating at a nearly fixed frequency Denervation (fibrillation) potentials were noted in the left sacrospinalis muscles opposite L_2 in patient R.H , a forty-two-year-old man with rheumatoid spondylitis of ten years' duration. The tracing has unfortunately been lost, but two responsible observers agreed that the spike characteristics observed on the oscilloscope were incompatible (duration 1 to 3 milliseconds) with motor unit activity We have not had an opportunity to reexamine the patient. Tremor patterns are frequently observed. The frequency is variable, usually 6 to 8 per second Tremor bursts often merge unexpectedly into sustained tetani They may be brought out by increased effort, as by lifting a weight. In some instances, tremor seems identical with fatigue and anxiety (neurosis) tremors seen in nonarthritic subjects.

COMMENT

It was not anticipated that electromyography would provide any sort of specific diagnostic or prognostic pattern All the findings might have been predicted in view of histologic abnormalities which have been reported by Morrison et al[1] and by other pathologists. A rheumatoid granuloma lying in a nerve trunk might well set up irritant foci of spontaneous discharges in neighboring axons If an examining needle by chance happened to be placed near a muscle fiber whose motor axon had undergone complete degeneration, fibrillation spikes might be observed, as we indeed observed The chance of such a lucky shot is remote, however It should be emphasized that the electromyographic examination often reveals no abnormal changes at all

The difficulty of distinguishing spasm, contracture, and fibrosis is well illustrated by the experience with patient C.G. This woman, with old arthritis of the hips, had had vitallium mold arthroplasties performed on both joints five years previously Her limitation of hip abduction was ascribed to spasm of the adductors. Electromyographic tracings from these muscles showed no activity during stretching Because of the almost bony [illegible]

exact site of the needle electr[illegible] muscle. The final interpretation, therefore, was pathologic shortening, or contracture.

The mechanism of tremor in normal (voluntarily produced) and pathologic states is well discussed by Bishop, Clare, and Price.[3] The constant

guarding activity of muscles in relation to a painful joint provides a physiologic basis both for the observed failure to relax and for the fatigue which is such a prominent and often early symptom of the disease. Tremor might then be interpreted as resulting from fatigue Whether the extensive muscle atrophy can also be ascribed to overwork of the muscles is a much more difficult problem concerning which we are unable to express an opinion. It is most unlikely, from our experience, that such atrophy is produced in any significant degree by denervation of muscles

For control observations we have examined large numbers of normal persons and the five other cases of nonrheumatoid disease previously mentioned, as well as many cases of neurologic disease Random spontaneous spikes and sometimes rhythmically repeating motor units are rarely observed in relaxed normal subjects, the incidence is probably far less than that observed in rheumatoid arthritis Spontaneous resting activity was noted by Morrison et al[1] in a case of gonococcal arthritis, clearly indicating the nonspecificity of this finding We noted no abnormalities in our control cases of arthritis (gonococcal, meningococcal, group-collagen, and degenerative). The control patient with frozen shoulder showed evidence of contracture of the pectoralis major, exactly similar to patient E B with combined frozen shoulder and rheumatoid arthritis

We did not utilize the technic of Buchthal and Clemmesen[4] for determining the presence or absence of synchrony Experience with normal subjects in this laboratory has led us to distrust this procedure

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ABSTRACTS

RESECTION ANGULATION OPERATION (RAM) FOR ARTHRITIS OF THE HIP

HENRY MILCH

The treatment of arthritis of the hip presents one of the many still unsolved problems of medicine Until the rheumatologist shall, in good time, discover a specific cure for the disease, the painful, deformed hip with limited or absent motion must continue to be submitted to surgical relief In the past, many types of arthrodesis which seemed to offer relatively simple means of treatment of the painful hip have been devised Increasing experience has, however, demonstrated that in over 30 per cent of the successfully fused cases, whether young or old intractable pain in the lumbar region was a sequel of the hip fusion

The author's method involves no effort at reconstruction of the anatomic configuration of the hip joint It is based on the concept that the criteria of a successful therapy are kinesiologic and not anatomic In the hip, perhaps more than in any

other joint in the body, this is predicated upon a restoration of mobility without loss of the essential stability The former objective is accomplished by resection of the diseased head and neck, the latter by angulation osteotomy in the coronal plane (Schanz type)

The operative intervention is exceedingly simple It is accompanied by relatively little shock and may therefore be indicated in older patients No plaster immobilization is used and the patient may consequently be permitted out of bed, walking with the aid of crutches within three to six weeks after operation No stiffness of the knee and ankle has been observed

Originally performed in two stages, the earlier operation has been completely

location, fracture of the femoral neck with avascular necrosis or arthritis, in ad- vanced osteoarthritis and in one case in which a previous arthroplasty had been completely unsuccessful In all cases stability and mobility have been restored, provided the motor power of the hip muscles has been adequate In several cases some pain has persisted, in one case this was overcome by the resection of the obturator nerve, in two others by removal of the projecting screws On the whole the patients have expressed themselves as happy and the results have been sufficiently encouraging to warrant wider use of the method

FUNDAMENTAL INVESTIGATIONS ON THE SYNOVIALIS, A NEW APPROACH TO THE NATURE OF ARTHRITIS

C I REED, NORMAN R JOSEPH AND IRVING E STECK

Fully recognizing the systemic nature of rheumatoid arthritis, we have undertaken a study, with new technics, of the fundamental physiology of the element most commonly involved in these systemic reactions. the synovialis

Some earlier efforts had been confined to single static determinations in vitro or in vivo Our experiments were done in continuity to permit following the reaction over a long period of time Another electrode inserted in the femoral vein made possible simultaneous continuous study of the changes in the blood from the general region This study was of value in the evolution of our procedures, involving many factors integrated in varying proportions under different conditions

The next step was to study the influence of vasomotor control by means of peri-

stimulation.

By this time it had become apparent that the synovial membrane is an actively metabolizing tissue Consequently, it appeared feasible to study membrane potentials and the influences of various ions thereon This led directly to a study of enzyme systems When known enzyme inhibitors or activators were injected while the potential was being determined, it was possible to get a quantitative picture of the metabolic reactions occurring In general, positive millivoltage indicates a quiescent state or at least a less active state, while negative potential indicates greater activity

Further studies are under way to determine how these facts may be integrated and modified in relation to pathologic changes in the joints preliminary to arthritis.

SPECIFIC INFECTIOUS ARTHRITIS

THE TREATMENT OF GONORRHEAL ARTHRITIS WITH PENICILLIN

NORMAN SPITZER, OTTO STEINBROCKER AND H HAROLD FRIEDMAN

This report is an evaluation of the effectiveness of penicillin in the treatment of twenty-eight cases of gonorrheal arthritis observed at Bellevue Hospital, New York City, over a period of three years

CLINICAL MATERIAL

In twenty-three of the twenty-eight cases a presumptive diagnosis of gonorrheal arthritis was based upon the clinical picture and course, together with the finding of a definite gonococcal infection in the genitourinary tract In the other five cases the diagnosis of gonorrheal arthritis was considered established since positive cultures were obtained from the joint fluid

TREATMENT

All patients received penicillin as soon as the diagnosis was made The average duration of the disease before hospitalization was seven days The length of penicillin therapy varied from three to thirty days in individual cases, with a total dosage of from 500,000 to 9,300,000 units

RESULTS

The results of treatment in these cases were evaluated according to the response of the arthritis, since in all twenty-eight cases a bacteriologic cure was obtained. Patients were classified as "cured," "greatly improved," and "not improved" or "failures," according to the following criteria "Cured" patients were those with completely restored joints "Greatly improved" patients were those in whom the following were observed First, fever, if present, quickly subsided, second, signs of acute joint inflammation such as pain, swelling, redness and heat promptly resolved or were markedly alleviated, and third, the residual joint involvement consisted only of slightly limited motion or tenderness "Not improved" or "failures" were those patients who showed residual deformity or in whom no apparent change in the joint involvement was noted during the course of penicillin therapy

Using these criteria, eight of our patients were cured, fifteen were greatly improved, and five were not improved

COMPARISON WITH OTHER FORMS OF THERAPY

In order to better evaluate penicillin therapy in gonorrheal arthritis, we thought it worthwhile to make a comparison between these results and those obtained in the past with this and other forms of therapy The methods that have been employed fall into four major categories non-specific and symptomatic therapy, hyperthermy sulfonamide therapy, and penicillin therapy

Nonspecific methods consisted of sedation, bed rest, application of heat

to joints, articular drainage, the parenteral use of various protein derivatives of the gonococcus, nonspecific foreign protein therapy and intravenous antiseptics. On the whole the results were poor with these modalities. Duration of the disease was prolonged and permanent articular damage occurred in at least 25 per cent of the cases.

Following the use of fever therapy in the early 1930's a marked improvement in results occurred. A comprehensive summary and comparison of the outcome of hyperthermy and the previous nonspecific therapy in the same hospital had been given by Schnabel and Fetter. In two series of ninety-three cases each, fifty-four were completely cured by fever, as against only five cures with nonspecific methods. Summarizing the status of fever therapy in the treatment of gonorrheal arthritis, Hench stated that if early and adequate treatment is given, patients have an 80 per cent chance of being cured, with an additional 10 per cent chance of being greatly relieved When the disease was of over six weeks' duration, the proportions of cure and great relief dropped 30 per cent and 35 per cent, respectively, with permanent ankylosis and stiffness common

With the introduction of the sulfonamides, it soon became apparent that the results with this therapeutic measure were at least equal to those previously obtained with hyperthermy. In early acute cases, 80 to 85 per cent recovery or marked improvement was obtained, although the duration of the disease continued to be prolonged. Fever therapy, therefore, became of secondary importance, with its use reserved for those cases resistant to the sulfonamides According to one observer, even sulfonamides have lost their former effectiveness in gonorrheal arthritis, with the incidence of failures having gradually risen from 15 per cent to 35 per cent or even higher. This has been attributed to the killing off of most of the sensitive strains, so that present-day gonorrheal arthritis is presumably largely due to sulfonamide-resistant organisms.

The first report of the use of penicillin in gonorrheal arthritis appeared in 1943 Since that time several other reports have appeared, but the most comprehensive series to date has been that of Hirsch, Feffer, and Dowling They reported seventeen cases of proved gonorrheal arthritis. Of these, fifteen were acute and of less than one month's duration The first seven of these acute cases received 200,000 to 2,400,000 units of penicillin in eight to thirty hours. In this group the genitourinary focus cleared promptly, but there was no improvement in the arthritis The authors stated that "all subsequently recovered on symptomatic measures, sulfonamides or fever therapy." The next group of eight acute cases received 1,000,000 to 2,000,000 units of penicillin over a period of five to ten days All showed complete recovery of joint function. The authors believed that the prolongation of the treatment in the second group of acute cases accounted for the good results

Although the twenty-eight cases herein reported provide too small a series for statistical analysis, the results in twenty-three of the twenty-eight cases, eight of whom were cured and fifteen of whom were greatly improved, showed a trend toward therapeutic effectiveness at least equivalent to, or greater than, the outcome from sulfonamide or fever therapy, and far superior to the older nonspecific forms of treatment. Furthermore, the duration of the disease was appreciably shortened

COMMENT

Certain of our observations we believe are worthy of further comment It is to be noted that in all of our patients a bacteriologic cure was effected However, our experience indicates that the attainment of a bacteriologic cure does not eliminate the need for attaining two other goals, namely, symptomatic relief and the prevention and correction of deformity. Thus, in ten of the last twelve cases followed personally by us, residual joint involvement had to be treated for an average of three weeks even though penicillin eliminated active gonococcal infection. The joint signs and symptoms in these cases were due to thickened, persistently inflamed synovial membranes, inflamed extra-articular structures or damaged cartilage surfaces. The therapeutic problem then, as in the chronic arthritides, revolves about the proper use of immobilization, movement, the various physiotherapeutic modalities, and corrective orthopedic procedures in order to obtain a musculoskeletal cure

The advent of the antibiotics, with their demonstrated effectiveness against the etiologic agents of certain specific joint infections, probably requires a revision of the methods of management of these cases The principles of prolonged rest and immobilization of infected joints to assure fixation in optimum positions served their purpose when specific infections

infection is under control, more attention must be given to the early and judicious use of physical therapy and exercise in increasing amounts, but within the limits of the patient's tolerance The adequate use of posterior molded splints, rather than prolonged immobilization, seems more suitable

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THE RELATION BETWEEN HEPATITIS AND POLYARTHRITIS

INGER-LOUISE MARNER

In 1897 George Still called attention to the fact that during the course of intercurrent hepatitis an improvement of the joint symptoms might be seen in cases of chronic rheumatoid arthritis In apparent contradiction to this it happens, although rarely, that chronic rheumatoid arthritis may arise after, or in immediate connection with, hepatitis A third circumstance, often observed during recent years in infectious hepatitis, is that some cases of hepatitis are introduced by arthritic symptoms lasting from days to months Those symptoms are not characterized only by pains in the joints, but also by swellings, so that clinically they may simulate true rheumatoid arthritis When the hepatitis of these patients then manifests itself, the rheumatic symptoms usually disappear

Several investigators, especially Hench, have attempted to find the cause for the beneficial effect which hepatitis can have on the symptoms of the

joints in rheumatoid arthritis Thus, studies have been made to determine whether the cause might be the increased amount of bilirubin or bile salts, or both these factors combined Some investigators think that the improvement is caused by the increased blood supply in the joints, which is seen in some patients with diseases of the liver.

As previously stated, chronic rheumatoid arthritis rarely develops in connection with hepatitis. Lundgren, in 1945, by going through the records of the Swedish invalid compensation bureau, found only 2 cases out of 2183 where the chronic rheumatoid arthritis had arisen in connection with hepatitis. I myself am able to describe one case. It concerns a sixty-two-year-old woman who had not previously had any joint disease. During a serious attack of hepatitis with a strong positive Takata-Ara reaction, after she had been icteric for one month there developed large cushion-shaped swellings of both hands and also swellings of the ankles During her stay at the hospital, which lasted three months, she was treated with massage, but later a typical chronic rheumatoid arthritis developed, with deformation of the finger joints and the ankles Reactions to both the Takata-Ara test and the thymol turbidity test were strongly positive a year and a half after her discharge, which indicates that chronic hepatitis had developed in addition to the chronic rheumatoid arthritis

The frequent occurrence of hepatitis during recent years in all medical departments in Scandinavia has led to some observations of the clinical features of this disease Thus, it has been noted that the initial rheumatic symptoms are frequent This feature of the disease was first noted by Graves in 1864, who called attention to the combination of acute rheumatoid arthritis, hepatitis and urticaria (nettlerash). It was not until many years later that descriptions of similar cases with pronounced initial joint afflictions were published, so that the question arises whether these initial symptoms of rheumatoid arthritis are phenomenona which alternate with the different epidemics, like the variations seen in other virus infections

A study of the records of 485 patients who, in the course of a year and a half, had been treated for hepatitis at two of Copenhagen's municipal hospitals, revealed that sixty patients (12 per cent) had had symptoms of the joints in the pre-icteric period As the patients are not systematically asked about this symptom in the recording of the history, 12 per cent is a minimum.

In order to supply the information for the record, I issued questionnaires to those sixty patients From the fifty-three replies (forty-two women and eleven men) the following information was obtained.

Duration of arthralgia before the appearance of the icterus was most often about one month In 70 per cent of the patients both large and small joints were affected simultaneously

In 49 [illegible] This swelling, as [illegible] n single instances [illegible]

There [illegible] ithema in 5 per cent.

That the pains were not negligible is indicated by the large number of patients, 72 per cent, who had taken analgesics on account of the afflictions of the joints.

Sixty per cent had consulted a physician on account of the rheumatic

symptoms, and 19 per cent had been hospitalized under the diagnosis "rheumatoid arthritis".

The treatment used varied considerably: sulfa preparations, salicylates, gold treatment, penicillin, diathermy, massage, heat and packings had been applied.

As soon as the jaundice became evident the symptoms in the joints disappeared or almost disappeared. Only one patient stated that the pains in the joints increased when she became icteric.

When the questionnaires were issued eight of the fifty-three patients still had pains in the joints, one to fourteen months had then elapsed since the cessation of the icterus.

In eleven of these patients the antistreptolysin titer has been estimated. In two cases it was increased, in one case slightly increased (200), in the other it was 600. This last mentioned patient had had tonsillitis three weeks before, accompanied by high temperature, but when she became icteric her joint symptoms disappeared.

In fourteen of these patients a complete blood examination was made, but no abnormal conditions were found.

In a number of cases of acute rheumatoid arthritis it may be important to bear in mind the possibility that a supposed rheumatic fever may turn out to be the forerunner of hepatitis, in order to recognize the affection of the liver as soon as possible and thus plan the treatment accordingly.

It must be suggested that the initial affections of the joints and the histologic changes in the liver during hepatitis are different reactions caused by the same virus.

GOUT

THE ROLE OF THE ANTERIOR PITUITARY AND THE ADRENAL CORTEX IN URATE METABOLISM AND IN GOUT*

WILLIAM D ROBINSON, JEROME W CONN, WALTER D. BLOCK,
LAWRENCE H. LOUIS AND JOSEPH KATZ

A definite increase in the urinary excretion of urates has been reported to follow the administration of 11-oxysteroids and pituitary adrenocorticotropic hormone (ACTH) to human subjects [1, 2] The present study was undertaken in an effort to define the mechanisms involved The results indicate that purine metabolism is profoundly influenced by the adrenal cortical hormones, and that these endocrine factors appear to be important in clinical gout.

CLASSIFICATION OF STEROIDS PRODUCED BY THE ADRENAL CORTEX

Advances in knowledge of adrenal cortical function indicate that the steroids produced by this gland can be classified in three main groups, according to their biologic effects

1 The sex-like steroids, estrogenic and androgenic The chief metabolic effect is positive nitrogen balance † These can be measured by biologic methods, or the end products of androgenic steroids can be measured by chemical determination of 17-ketosteroids †

2 The 11-oxysteroids, which can be imperfectly estimated by chemical methods, and produce the following metabolic effects

   a Negative nitrogen balance †
   b Depression of carbohydrate tolerance †
   c Increased urate excretion †
   d Changes in blood cellular elements, including a decrease in circulating lymphocytes and eosinophils †

3 The desoxycorticosterone-like steroids, which cannot be measured directly Metabolic effects are retention of water, sodium and chloride, and loss of potassium, changes in body weight† and urinary excretion of electrolytes† reflect imperfectly the activity of these steroids, concentration of sweat electrolytes is a better index of their activity [3]

METHODS

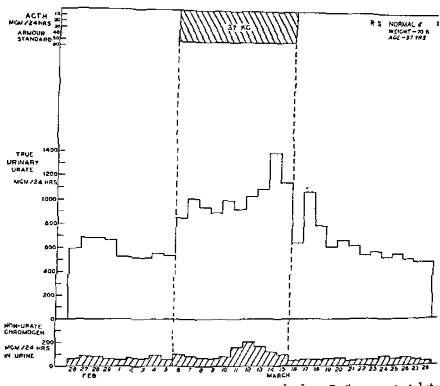
In the metabolic studies, all subjects were on a constant diet, containing 99 gm of protein, 300 gm of carbohydrate and sufficient fat to maintain adequate caloric intake, the purine intake was moderate, but constant The

* From the Department of Internal Medicine and the Rackham Arthritis Research Unit University of Michigan Medical School Ann Arbor Michigan The Rackham Arthritis Research Unit is supported by a grant from the Horace H Rackham School of Graduate Studies This study was supported in part by grants from the Eli Lilly Company and the Research Grants and Fellowship Division of the United States Public Health Service

† Methods marked with dagger were used in these studies Details regarding methods of determination are cited in previous communications [4, 5]

purified pituitary adrenocorticotropic hormone (ACTH) was prepared a modification of the method of Sayers and associates[6] in the Arm Laboratories, Chicago.* Dosage is expressed in terms of the Armour AC standard as determined by bio-assay; the lots used in these studies identified in the figures.

Figure 68 illustrates the study plan used: After a control period, sub R S. received approximately 50 mg per day, in three equal doses e



24 hours

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for the nonspecificity of colorimetric techniques by determining the reduc tion of chromogenic activity after the action of the enzyme, uricase, whicl specifically destroys uric acid This is designated as the true urate value It also determines those materials which give color reactions with the uri acid reagents which are not destroyed by uricase. This is designated a: nonurate chromogen and expressed as the chromogenic equivalent of uri acid

* We are indebted to Dr J. R. Mote, The Armour Laboratories, Chicago, for the ACTH used in these studies

RESULTS

Effects of ACTH on Metabolism of Normal Subjects In normal subject R S, hormone administration resulted in a prompt increase in true urate excretion which persisted throughout the injection period, reaching its peak on the ninth day There was an increase in nonurate chromogen, which appeared later and was not well sustained There was a pronounced drop in true urate excretion on the first postinjection day, followed by unusually high values on the second and third postinjection days, after which the

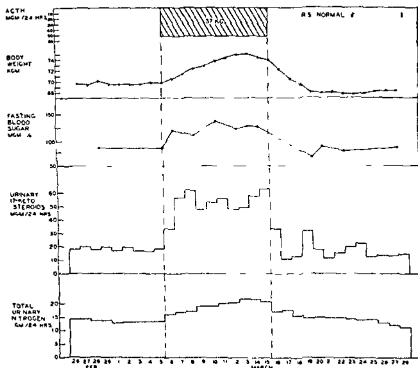


Fig 69 Effect of ACTH on other indices of adrenocortical function in normal subject R S Additional metabolic data on this study published elsewhere [4]

values did not differ significantly from the preinjection control period Blood urate content was not followed by the uricase method on this subject, by the direct method of Brown[9] apparent urate content fell from 3 1 mg per cent to 2 4 mg per cent during the ten-day period, rising to 3 2 mg. per cent by the eighth postinjection day

Figure 69 indicates some of the [illegible]

ing

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excretion occurred with ACTH administration, dropping promptly after the first twenty-four hours after medication was stopped, but with a sharp increase on the fourth postinjection day. This, together with the rise in

urate excretion seen in Figure 68 and changes at times in carbohydrate tolerance, is interpreted as evidence of a rebound in endogenous pituitary-

elsewhere[4, 5] The changes in fasting blood sugar are charted as an index of this effect Definite retention of fluid and electrolytes also occurs. This

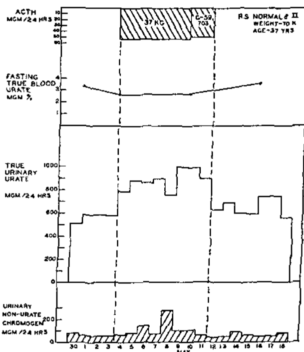


Fig 70 Effect of ACTH on blood and urine urate of normal subject R S. in second study during which protamine zinc insulin was also administered Diet as noted for Fig 68 Additional metabolic data on this study published elsewhere[5]

is represented by the changes in weight, which were accompanied by the expected changes in urinary sodium and chloride excretion

Injection of desoxycorticosterone acetate in doses of 20 mg. daily to a normal subject for ten days did not produce any effects on purine, nitrogen or carbohydrate metabolism

Figure 70 illustrates the changes in urate metabolism in a second study on normal subject R S Protamine zinc insulin, administered during the period of ACTH injection, modified the effects on carbohydrate metabolism[5] but did not alter the pronounced increase in urinary excretion of urates or nonurate chromogen A rebound in urate excretion is noted on the second, fifth and sixth postinjection days. The apparent blood urate level by the direct method fell from 3.2 to 2.2 mg per cent during hormone administration, however, the blood urate as determined by the uricase method was

not significantly altered The direct methods for uric acid are known to be influenced by nonurate reducing agents in the blood, such as glutathione.[8] Conn and associates[5, 10] have demonstrated a decrease in these materials during ACTH administration

Figure 71 illustrates similar changes in normal subject D E. induced by a different batch of ACTH Due to error in original assay of the potency of this material, only one-half of the actual dose previously used was administered the first three days to this subject. The magnitude of urate increase is not as great, but rebound in urate excretion on the second and fifth postinjection days, as well as the inconstant rise in level of nonurate

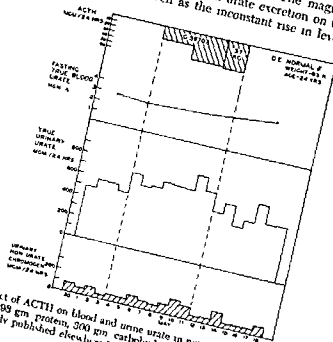


Fig 71 Effect of ACTH on blood and urine urate in normal subject D E on constant diet containing 99 gm protein, 300 gm carbohydrate, 176 gm fat Additional metabolic data on this study published elsewhere[6]

chromogen excretion, was again noted. Again there was no drop in the blood urate as determined by the uricase method, although by the direct method there was a fall of 1 2 mg per cent These findings are in accord with the data of Thorn and associates,[2] who found the increase of urate excretion during ACTH administration could not be accounted for solely on the basis of increased renal excretion, and postulated that the hormone must actually increase urate production in the normal subject

Effects of ACTH on Metabolism of Gouty Subjects The nature of the metabolic defect in gout accounting for the elevation of blood uric acid has never been identified Explanations have centered around an increase in uric acid production, or a specific impairment in renal excretion of uric acid These considerations led to a study of the effect of ACTH on a patient with pretophaceous gout who has been under observation for eight years This forty-two-year-old man has for ten years had repeated attacks of

acute gouty arthritis observed to *respond to colchicine*; his serum urate level has ranged from 6 5 to 9 5 mg. per cent. His liver and kidney function is normal by standard tests

Administration of ACTH for five days (Fig. 72) resulted in a prompt increase in urinary urate excretion comparable in magnitude to that *seen* in normal subjects. In contrast to the normal subjects, this was associated with a marked fall in true blood urate, reaching a low of less than 50 per cent of the control level on the morning of the fourth day of hormone ad-

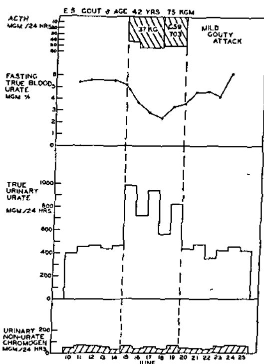


Fig 72 Effect of ACTH on blood and urine urate in gouty subject E S on constant diet of 99 gm protein, 304 gm carbohydrate and 178 gm fat Urinary creatinine averaged 1 50 gm per 24 hours

ministration This suggests that increased renal excretion accounted for a great portion of the augmentation of urinary urate output in the gouty patient, whereas in the normal subjects the entire increase may be attributed to increased urate production Quantitative calculations regarding changes in total body urate cannot be made until accurate information is available concerning the partition of urates in body fluids Using the estimates of "urate space" obtained by Benedict, Forsham and Stetten[11] in their studies with isotopically labelled uric acid, calculations of these data indicate an increased production of urate under the influence of ACTH in the gouty patient as well as an increase in clearance by the kidney. This subject also differed from the normals in showing no rise in nonurate chromogen and no rebound in urate excretion during the postinjection period

The other metabolic effects during ACTH administration were roughly similar to those seen in normal subjects (Fig 73) Increase in urinary

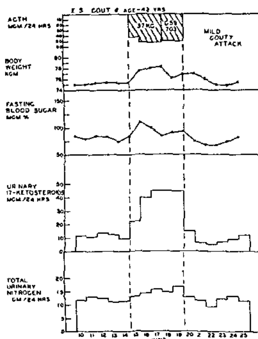


Fig 73 Effect of ACTH on other indices of adrenocortical function in gouty subject E S Additional metabolic data on this study published elsewhere[6]

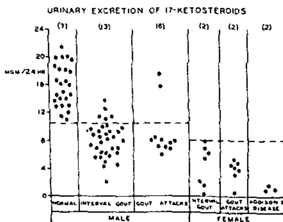


Fig 74 Excretion of 17-ketosteroids[14] in normal subjects and in patients with gout and Addison's disease Figures in parentheses indicate number of subjects in each group

nitrogen occurred Ability to respond to the hormone with 17-ketosteroid production appeared normal Impairment of carbohydrate utilization was definite, although not as well sustained as in the normal subjects. Retention of fluid and electrolytes was observed. Conspicuously absent was any evidence of rebound in pituitary-adrenocortical activity. In fact, the 17-

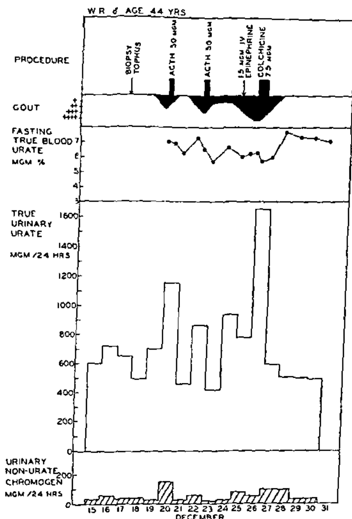


Fig. 75. Blood and urine urate levels during gouty attack following tophectomy, temporarily suppressed by ACTH, unaffected by intravenous epinephrine, terminated by oral colchicine. Diet constant, furnishing 82 gm protein, 316 gm. carbohydrate, 107 gm fat. Urinary creatinine averaged 1.40 gm per 24 hours

ketosteroid excretion was lower than observed in any other subject during this period, averaging about one-half of the control values on the *second* to fourth postinjection days.

This subject, who had been free of symptoms for the preceding nine months, experienced mild but definite gouty attacks on the third to fifth postinjection days, at a time when the studies suggest a decrease in adreno-

cortical activity. In 1935 Talbott and associates[12] described cyclic changes in urate, water and electrolyte excretion in patients with gout, and noted a diuresis of sodium and chloride immediately before or on the day of maximum articular distress. Their data can be interpreted as reflecting cyclic changes in adrenocortical activity, with attacks occurring during periods of decreased function It is noteworthy that this patient had his maximum urinary excretion of sodium on the second and third postinjection days

While these studies were in progress, Wolfson and associates reported findings of low excretion of 17-ketosteroids in gouty patients [13, 14] We have

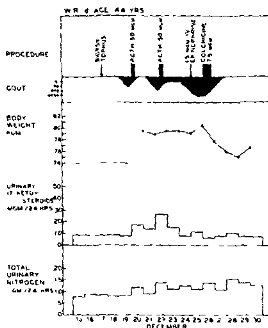


Fig 76 Other indices of adrenocortical function during gouty attack in subject W R.

confirmed their observations (Fig 74) Twenty-five determinations on seven normal male subjects gave values ranging from 10 5 to 22 mg per twenty-four hours Only five of thirty-four determinations on thirteen gouty males during asymptomatic periods exceeded 10 mg per twenty-four hours Nine of eleven determinations on six subjects during attacks were below this level There was no tendency for the level to be lower or higher in the same subject during attacks as compared with interval values Particularly interesting are the levels in two gouty women, where the gonadal contribution to the 17-ketosteroids is eliminated. Repeatedly low values

gout was afforded in patient W R, who developed acute gout forty-eight hours following removal of a tophus under local anesthesia (Fig 75) The

nitrogen occurred. Ability to respond to the hormone with 17-ketosteroid production appeared normal. Impairment of carbohydrate utilization was definite, although not as well sustained as in the normal subjects. Retention of fluid and electrolytes was observed. Conspicuously absent was any evidence of rebound in pituitary-adrenocortical activity. In fact, the 17-

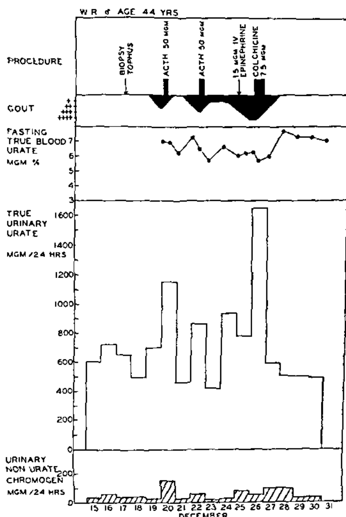


Fig 75. Blood and urine urate levels during gouty attack following tophectomy, temporarily suppressed by ACTH, unaffected by intravenous epinephrine, terminated by oral colchicine. Diet constant, furnishing 82 gm protein, 316 gm carbohydrate, 107 gm fat. Urinary creatinine averaged 1 40 gm per 24 hours

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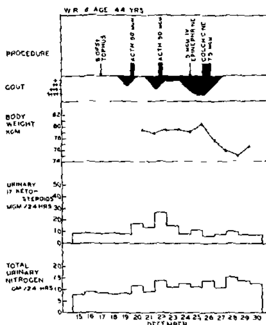
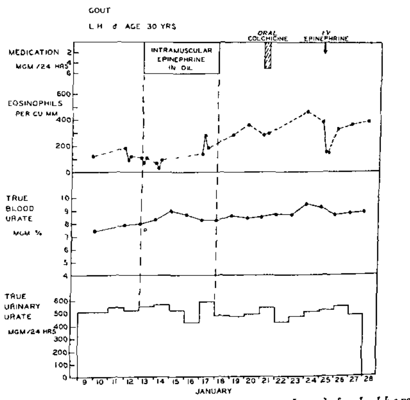


Fig 76 Other indices of adrenocortical function during gouty attack in subject W R

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An opportunity to observe the effects of ACTH during an acute attack of gout was afforded in patient W.R, who developed acute gout forty-eight hours following removal of a tophus under local anesthesia (Fig 75). The

period prior to the attack was not characterized by any alteration of urate excretion Fifty mg of ACTH, given intramuscularly within eight hours, was followed by a temporary relief in acute joint manifestations lasting twenty-four hours, and changes in blood and urine urates indicated stimulation of adrenocortical activity. With recurrence of symptoms, ACTH was again followed by symptomatic relief and similar metabolic changes However, symptoms recurred and extended to the knee, previously uninvolved Our reasoning at this time was as follows: The evidence was suggestive



of adrenocortical suppression at the time of acute attacks, yet these glands appeared capable of responding to ACTH, both in interval periods and during attacks Therefore, the decreased activity is likely to be at the pituitary level Exogenous ACTH should benefit the situation temporarily, but may at the same time depress endogenous pituitary activity, so that when its effect has worn off, the patient's own pituitary *is unable* to take over It was logical to attempt to stimulate pituitary activity directly. Intravenous epinephrine, reported by Recant and coworkers[16] to have such an effect, was given, during the next twenty-four hours there were no definite metabolic changes and the gouty symptoms became much more severe The attack was then terminated by oral colchicine, symptomatic relief was

associated with a spectacular increase in urate excretion, and a profound diuresis.

Other metabolic effects observed are indicated in Figure 76 Increase in urinary nitrogen excretion followed each administration of ACTH, during the later attack period definitely negative nitrogen balance was present. This has been a consistent observation in all gouty attacks studied in our laboratories The 17-ketosteroid excretion was unaltered prior to the attack, definitely increased after each ACTH injection, and was not altered after

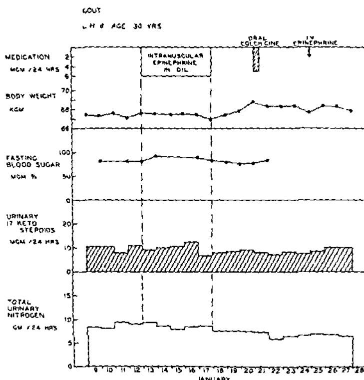


Fig 78 Other indices of adrenocortical function during study on gouty subject L H

epinephrine or colchicine Fasting blood sugar levels were not altered significantly, and glycosuria did not occur The magnitude of diuresis associated with termination of the attack with colchicine is indicated by the body weight loss of 2 7 kg in twenty-four hours.

Independent observations by Hellman[17] on the effect of ACTH have given similar results with respect to provocation of attacks and relief during attacks An important difference was his observation that ACTH, in larger doses and over a longer period of time, could terminate acute attacks.

Effects of Epinephrine and Colchicine on Metabolism of Gouty Subjects Time relationships in the above study do not permit us to tell whether the

period (Fig. 77). Epinephrine in oil, given in divided doses of 6 mg daily for five days, produced no definite alterations in blood or urine urate levels The level of circulating *eosinophils was depressed during the first two days* of this administration. Oral colchicine, in dosage of 0 5 mg. every hour to a total of 5 mg , produced no effect on urate levels or eosinophils. Two mg of epinephrine given intravenously in one hour produced the expected sharp drop in eosinophils, but had no effect on urate levels No gouty symptoms developed at any time during these studies.

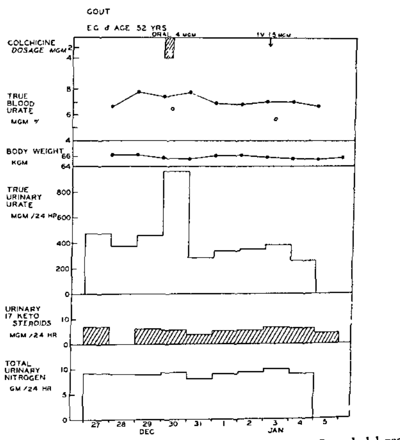


Figure 78 indicates the absence of any other evidence of adrenocortical stimulation in this subject by these procedures. Urinary nitrogen was not *clearly altered*, 17-ketosteroid excretion remained low throughout, fasting blood sugar levels were not clearly influenced, and body weight showed no consistent fluctuations.

In studies on four additional gouty subjects, colchicine administration in oral doses of 4 to 5 mg and intravenous doses of 2 0 mg. has not affected either the level of circulating *eosinophils or of 17-ketosteroid* excretion In one additional subject, however (Fig 79), we have observed a marked increase in urate excretion following oral colchicine during an asymptomatic

period. This was not accompanied by a drop in blood level, nor any change in 17-ketosteroid or nitrogen excretion. A few days later 1 5 mg intravenously produced no effect. Such an increase in urate excretion is contrary to reported effects of colchicine, and to previous experience in our laboratory. All our previous observations, however, have been made during acute gouty attacks

Certainly colchicine does not produce the complete metabolic alterations seen consistently after administration of ACTH. The possibility of selective stimulation of the endocrine mechanism cannot be ruled out

COMMENT

These observations are obviously of an incomplete nature and much more work is necessary to define accurately the mechanisms involved. They are reported at this time for two reasons. (*a*) to call the attention of those investigators who have access to the limited supply of ACTH to what appears to be a promising field of investigation, and (*b*) to indicate the necessity of considering endocrine factors in the interpretation of metabolic studies on gouty patients.

CONCLUSIONS

Tentative conclusions to date are (*a*) The adrenal cortex has a profound influence on urate metabolism, (*b*) its effect in gouty patients differs somewhat from that in normal subjects, (*c*) gout is characterized by a low excretion of 17-ketosteroids; and (*d*) the adrenal cortex of gouty patients can respond to exogenous ACTH stimulation, both during interval periods and at times of acute attacks

There is suggestive but not conclusive evidence (*a*) that acute attacks tend to occur at times of decreased adrenocortical activity, and (*b*) that the latter is the result of sluggish production or activation of endogenous ACTH under the same conditions in which normal people demonstrate evidence of a sharp increase in activity of endogenous ACTH Epinephrine appears to be an unsatisfactory method of stimulating pituitary-adrenocortical activity in gouty patients. The mode of action of colchicine through an endocrine mechanism has not been established

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THE FUNDAMENTAL ROLE OF ADRENAL CORTICAL DYSFUNCTION IN THE PATHOGENESIS OF GOUT*

An Endocrine Basis for the Rapid Treatment of Acute Gouty Arthritis with Pituitary Adrenocorticotropin (ACTH) and Colchicine

WILLIAM Q. WOLFSON, CLARENCE COHN, RACHMIEL LEVINE, EDWARD F ROSENBERG, H DUNHAM HUNT AND HENRY S. GUTERMAN

The regular absence of obvious physical signs of endocrinopathy in patients with gout has delayed consideration of a possible endocrine background, even though gout has long been suspected of being an inherited constitutional disorder of metabolism The use of pure hormones for diagnostic testing, and newer techniques for determining glandular status by biochemical methods, have recently made possible the detection of endocrine disturbances although physical abnormalities are absent. Rapidly accumulating evidence† of hormonal dysfunction in gout is largely an outcome of these advances in basic endocrine physiology.

AN ABNORMAL MALE SEX HORMONE IN GOUT

17-Ketosteroid Excretion in Gout. One may suspect that androgens favor the appearance of clinical gout because of its predilection for adult men and its relative rarity in children, premenopausal women and eunuchs. The 17-ketosteroids (17-KS) are metabolites of adrenocortical and testicular androgens Their urinary excretion reflects the rate of androgen production under most circumstances.

In all gout patients studied, whether during the interval or in an attack,

* [illegible] Research [illegible] Research Council

† Our present understanding of adrenocortical dysfunction in gout is the outcome of [illegible] full citations here, [illegible] information with [illegible] the interpretation [illegible] Drs William D [illegible] M. Stecher, Leon Hellman, and their coworkers.

17-KS excretion was greatly reduced The average value (3 2 mg per day) was about one-third of the minimum normal value for adult men. Equally low 17-KS outputs did not occur in nongouty hyperuricemia or in men with rheumatoid arthritis or with spondylitis. Gout patients showed no signs of the *endocrinopathies known to cause very low 17-KS outputs, namely,* panhypopituitarism, Addison's disease and severe hypothyroidism

In spite of very low 17-KS outputs, the regular absence of hypogonadism in our gout patients made it apparent that some androgen was being secreted Injection of testosterone, now believed to be the most important normal male sex hormone, led to normal recoveries of extra-urinary 17-KS This showed a normal hepatic ability to convert injected androgens to ketosteroids It became necessary to conclude that the low 17-KS outputs resulted from the patients' failure to secrete adequate amounts of normal androgens rather than from an inability to convert androgens to ketosteroids Since normal androgens were being secreted in reduced amounts, it appeared that the hormone responsible for the maintenance of androgen activity in the gouty must be an abnormal male sex hormone which, when metabolized, was not importantly converted to urinary 17-KS.

The suggestion that there may exist an abnormal male sex hormone which is not metabolized to urinary 17-KS is not entirely unprecedented In women with arrhenoblastoma, a masculinizing tumor of the ovary, 17-KS outputs before operation may be normal or low, and, following successful resection of the tumor, 17-KS outputs may be unchanged Since gout may occur in men or women, the abnormal androgen in gout presumably originates in the adrenal cortex, which is the only site of androgen production common to both sexes at the usual age of onset of clinical gout Certain data suggest that a metabolite of this abnormal adrenocortical androgen may occur in the nonketonic fraction of the steroids isolated from gouty urine

[illegible]

average plasma urate level between the sexes However, adult men have higher plasma urate levels than adult women, both in the normal and gouty groups This normal sex differential in plasma urate is presumably a function of the normal androgens which attain adult rates of secretion during puberty

Genetic hyperuricemia, an inherited biochemical lesion of gout, is regularly present before the onset of clinical gout Carriers of this defect were found by Smyth, Cotterman and Freyberg to have normal plasma urate levels until puberty if male, and by Stecher, Hersh and Solomon to have normal plasma urate levels until the menopause if female To explain these

[illegible]

be inherited by either sex, this abnormal androgen presumably also originates in the adrenal cortex As a first assumption, it is convenient to identify the abnormal adrenocortical androgen responsible for the appearance of inherited hyperuricemia with the similar androgen detected by the study of 17-KS output in gout

11-OXYSTEROIDS* Recent reports show the 11-oxysteroids (11-OS) to be important regulators of urate metabolism The administration of a potent 11-oxysteroid, such as 17-hydroxy-corticosterone, or an increased adrenal 11-OS output, obtained by stimulating the adrenal with the adrenocorticotropic hormone (ACTH),† has two effects on urate metabolism· It increases urate production and urate clearance as well. The two effects are somewhat independent, and the increase in urate clearance is relatively deficient when the kidneys are damaged. In the normal adult, ACTH administration causes (a) either no change or some decrease in plasma urate, (b) an increase in the ratio of urine urate to urine creatinine, and (c) an increase in the ratio of urate clearance to creatinine clearance. In gout, the latter two changes are less marked than in normal adults, even when hematologic changes show a normal adrenal response to ACTH stimulation

Certain evidence suggests that plasma urate levels, absolute urate outputs and the renal clearance of urate depend upon the ratio of 11-OS activity to the activities of abnormal and normal androgens, rather than upon the absolute levels of either In those endocrinopathies in which the absolute production of 11-OS is increased (Cushing's syndrome and some acromegalics) the pattern of urate metabolism may resemble that of normal adults who have received ACTH.

In children, the absolute 11-OS production is not abnormally high, but 11-OS/androgen ratio is high owing to their small androgen secretion Children, however, also show the low average plasma urate level, and the high ratio of urine urate to urine creatinine and of urate clearance to creatinine clearance which are seen in the adult after ACTH. Preliminary observations suggest that the findings in normal children may assume the adult pattern after androgen administration The resemblance between the childhood pattern of urate metabolism and that produced in adults by ACTH suggests the 11-OS/androgen ratio, rather than the absolute levels of either, to be the effective determinant of urate metabolism

...al Adrenocortical Androgen Although ... cause the clinical symptoms of gout, ... most cases to be correlated with the *duration and severity of antecedent hyperuricemia* The abnormal adrenocortical androgen appears to regulate the time of appearance of inherited hyperuricemia in those genetically predisposed, and so appears basic to the susceptibility to clinical gout

A DEFICIENT RESPONSE TO 11-OXYSTEROID LACK IN THE GOUTY

...

reason, a particularly satisfying aspect of recent advances in the endocrin... ology of gout has been the indication that both aspects of the disease were under steroid control

Hormonal Induction and Relief of Acute Gouty Arthritis. Hellman, and

* *The term "11-oxysteroid" is here used* rather loosely to include both the glycocorti- ... metabolism and the

... our Laboratories, ... and for a number

Robinson and his associates, have reported that when ACTH was administered to patients with interval gout and then withdrawn, an attack of acute gouty arthritis has begun within ninety-six hours in most patients. Both groups have also observed relief of spontaneous gout attacks or attacks induced by ACTH withdrawal following the administration of ACTH

We have confirmed these findings and have also observed relief of a [illegible]

thirty-six hours and ended with the explosive onset of a severe polyarticular exacerbation in which virtually all of the joints of the appendicular skeleton were involved This observation suggests that the effects upon clinical symptomatology produced by ACTH, like its effects on urate metabolism, actually depend on the alterations in 11-OS output which ACTH produces

Withdrawal of ACTH, in the normal adult and in the gouty, is followed by metabolic changes indicating 11-OS lack These persist for a few days and in normal subjects are terminated by a short period of "rebound" 11-OS excess, following which function restabilizes at normal levels. In the gouty, rebound appears deficient and attacks induced by ACTH withdrawal begin at the time at which rebound normally would occur Presumably, this indicates that a sufficiently prolonged relative lack of 11-OS produces progressive metabolic changes which eventually provoke a gout attack in a predisposed individual and which may be reversed by 11-OS excess.

Adrenal Function During Spontaneous Gout Attacks Some years ago, Talbott and his associates at the Massachusetts General Hospital reported cyclic alterations of water and electrolyte exchange which suggested their concept of a "gout cycle" From metabolic studies, they found electrolyte turnover in the prodromal phase of the attack to resemble those of relative adrenocortical insufficiency.

Our studies, as well as long-available nitrogen metabolism data, appear to confirm Talbott's suspicion In the prodromal period before a spontaneous attack of acute gouty arthritis, metabolic findings indicate relative 11-OS lack, and these findings persist during the active stage in which the attack is developing As an attack subsides spontaneously, there may be metabolic evidence of relative 11-OS excess Prolonged attacks which resist therapy may give evidence of persistent 11-OS deficiency Most gout attacks are not precipitated by a known incitant and presumably arise from the periodic endocrine shifts of the intrinsic "gout cycle", however, induction of relative 11-OS deficiency does appear to be a reasonable common factor in the action of most of the known incitants of acute gouty arthritis In particular, that identical metabolic changes appear to occur whether attacks are spontaneous or precipitated by ACTH withdrawal indicates the essential similarity of the two varieties

The Action of Colchicine In animals, toxic doses of colchicine are known to increase the output of 11-OS, like many other toxic substances Some investigators have been tempted to explain the effect of colchicine in gout merely as due to the production of relative 11-OS excess.

Our findings indicate that a therapeutic dose of colchicine (1 or 2 mg intravenously) produces metabolic changes in the normal adult which indicate increased 11-OS production Nevertheless, it seems unlikely that this

increased 11-OS output is a complete explanation for the action of colchicine in gout Withdrawal of colchicine *after its administration to interval* gout patients does not precipitate acute gouty arthritis. Moreover, Landolt's recent report of a persistent thrombocytosis induced in man by single doses of colchicine, if confirmed, will show an effect of therapeutic doses of colchicine which is probably not mediated by ACTH, since ACTH has been reported not to affect circulating platelet levels.

The Defect in 11-Oxysteroid Production in Gout Lack of rebound after ACTH withdrawal, *Robinson's observation of failure of 11-OS* excretion to increase during an attack precipitated by ACTH withdrawal, failure to observe the eosinopenia or lymphopenia which would demonstrate increased 11-OS production during gout attacks; and our observation that sensitivity to a nominal dose of adrenal cortical extract was retained during a prolonged severe attack—all these suggest that the basic defect is a failure of the gouty to respond to relative 11-OS lack by prompt increase in 11-OS *production.*

Recent reports suggest an acute control of serum cholesterol level by the adrenals Factors which stimulate steroid hormone synthesis appear to cause an acute fall in serum cholesterol, while inhibition of steroid output with desoxycorticosterone or adrenal cortical extract is followed by an increase in serum cholesterol It is believed that the serum cholesterol is the ultimate substrate for adrenal steroid formation In gout, we have observed *an average fall of 63 mg per cent in serum total cholesterol during the active* phase of the attack This has seemed to occur prior to the change in other

tive 11-OS lack by a prompt increase in production may be either due to an *intrinsic adrenal defect or to a defect in trophic stimulation by the pituitary* The data do not yet permit a clear choice between the two possibilities

RAPID TREATMENT OF ACUTE GOUTY ARTHRITIS BY CONCURRENT *ADMINISTRATION OF ACTH AND COLCHICINE*

Acute gouty arthritis now appears to be a true endocrine deficiency state Attacks are precipitated by persistent 11-OS lack in a susceptible individual and may be terminated when the deficiency is repaired by giving ACTH When ACTH is withdrawn from a patient after his attack has been halted, one might expect to see the episode return since the endocrine deficiency now recurs Actually, in the combined experience of Hellman, Robinson and ourselves, this has been true in most, but not in *all cases. Nevertheless,* the recurrence of attacks following hormone withdrawal makes administration of

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ACTH withdrawal to precipitate a renewal of the attack Ten attacks have been treated by concurrent administration of ACTH and colchicine In *seven, a single 50-mg dose* of ACTH (Armour) effectively terminated the attack within four hours In three, a second or third dose was required at six-hour intervals after the first Although a number of the episodes treated had been prolonged and resistant to previous therapy, no ACTH-treated

attack has persisted more than twenty-four hours after hormone therapy was begun

[illegible]

colchicine for at least two weeks No patient who has received combined ACTH-colchicine therapy has had even a minor recurrence of acute gouty arthritis within one month of treatment

The concurrent administration of ACTH and colchicine appears to be the most rapid and effective available treatment for acute gouty arthritis In view of the relative scarcity of ACTH the small amounts of this hormone which are required constitute a particularly desirable feature

DISCUSSION

L MAXWELL LOCKIE

As Dr Savage has recently remarked, the low purine diet of the British today has reduced the incidence of gouty arthritis in England, and this may be the factor that raises the ability of the gouty patient to keep his 11-oxysteroid level up and thus prevent recurrences of gouty arthritis, or perhaps it enables the body to meet the demand for 11-oxysteroids as the occasion calls

The administration of a high-fat diet has been successful in provoking an acute attack of gouty arthritis in a high percentage of cases in our hands and in the hands of some others, it would be interesting to examine the data for any factors which are in keeping with a lower 11-oxysteroid production along with a constant increase in the blood urate level

It might be well at this point to emphasize again what the indices of oxysteroid production are, as outlined by Dr Wolfson (*a*) decrease in total eosinophils, (*b*) decrease in lymphocytes, (*c*) increase in total urate/total creatinine ratio, and (*d*) increase in urate clearance/creatinine clearance ratio. The inability of the gouty patient to meet the 11-oxysteroid demands is a serious one

It is of interest that diminished 17-ketosteroid excretion is characteristic of gout This is not found in rheumatoid arthritis, nor in idiopathic hyperuricemia Serum cholesterol esters might be the ultimate substrate for 11-oxysteroid formation Already, the conversion of isotopic cholesterol to a steroid hormone has been shown

Another interesting point illustrated here is evidence that colchicine acts by producing an ACTH effect through the pituitary gland Perhaps some of the other chemical substances which have a similar effect on mitosis might have the same effect Podophyllin is one of the easiest to use As the result of the work presented here it would seem logical that colchicine should be continued in small doses over long periods of time in the patient with gouty arthritis, especially of the stubborn variety

Robinson has shown the similarity between the ACTH effect and Talbott's observations of the disturbed water and electrolyte exchange of sodium and potassium salts before an acute attack of gouty arthritis and mild adrenal cortical insufficiency It should also be remembered that cortisone is a potent 11-oxysteroid

ABSTRACTS

GENERAL DISCUSSION ON GOUT

PHILIP S. HENCH, HUBERT J GIBSON, HALVARD HEGNA, L. MAXWELL LOCKIE, EDWARD F ROSENBERG AND OSWALD SAVAGE*

SEX INCIDENCE

Gout is much more frequent in men than in women The impression in England is that not more than 5 per cent of gouty patients are women *This differential has* long been recognized· Hippocrates stated that gout did not occur in eunuchs, and that women did not contract the disease until after cessation of the menses This latter observation is now known to be inexact, gout may occur in women before the menopause The difference in incidence between the sexes is presumably linked with the fact that values of urates become higher in men shortly after puberty, but this elevation in urate values does not occur in women until after the menopause

THE MECHANISM OF ACUTE GOUTY ARTHRITIS

There are many precipitating factors in gout, of which the commonest is trauma Psychologic upsets and allergic reactions may also play a part, although gout is [illegible]

[illegible]

is then withdrawn, the adrenal cortex functions at a lower level for a few days [illegible]

reaction to such a definite hemolytic toxin as lead might be just enough to precipitate a gouty attack

PATHOLOGY

The tophus is the characteristic lesion of gout. *Whether it occurs in subcutaneous* tissues, in cartilage or in synovial membranes, it consists of a central zone composed of crystalline urates and necrotic debris, and a surrounding inflammation

The histologic changes that take place in a joint during an attack of acute gouty arthritis are not known by direct observation However, the joint becomes hot and swollen, and it must be assumed that the synovial membrane is inflamed There is often a fluid exudate

Gouty arthritis is a very mixed arthritis having elements of osteoarthritis with synovial reaction, especially in the late stages It is the end result of chronic inflammation or irritation of all constituent structures of the joint It is a nonspecific arthritis apart from the deposition of crystals, which may be marked in the cartilage and in the subjacent bone

Clinically there is some involvement of the kidneys in gout In the prodromal

* The authors listed participated in a group discussion of which this is an abstract

phase of an attack there is a uric acid diuresis of about 25 per cent Gout is often associated with radiologically nonopaque renal uric acid calculi Chronic nephritis is one of the commonest causes of death in patients with gout The uric acid clearance rate in patients with well developed gouty arthritis is apt to be low. If such patients are put on a very high glucose diet the uric acid clearance rate may improve by a factor of as much as 2 5, whereas the urea clearance rate may increase very little. About 10 to 20 per cent of these patients have urate stones sometime during the course of the disease These patients have strokes, coronary attacks and other evidence of arteriosclerosis in a higher proportion of cases than will be found in a normal group.

DIAGNOSIS

[illegible]

nostic determinations of uric acid values it is necessary to be sure that the patient [illegible]

[illegible]

with a lens if necessary, there is seen any bone reaction or outlining of dense bone, it is not a true punched-out area, but is more suggestive of rheumatoid arthritis than of gout

THERAPY

[illegible]

upset, or when his gouty symptoms subside In general, colchicine is not toxic to [illegible]

ONE HUNDRED AND FIFTY CASES OF SCLERODERMA*

IRVING LEINWAND, A. WILBUR DURYEE AND MAURICE N RICHTER

Scleroderma is not a common disease but it is definitely not a rare disease The first description of this condition is credited to Curzio of Naples in 1752. Since that time there have been hundreds of cases reported in the literature

Scleroderma was first regarded as primarily a skin disease. Any systemic symptoms for the most part received scant attention since skin lesions far overshadowed any other complaints. However, defects in the peripheral circulation producing skin, color, and temperature changes, ultimately led to its inclusion in the peripheral vascular diseases A detailed study of the pathology of the disease necessitates its further disposition and reclassification as a generalized disease of the collagen system.

In reviewing the history of scleroderma, one is impressed by the metamorphosis of opinion regarding the classification of this disease This is due mainly to the obscurity of its etiology and the myriad of theories attendant upon such a situation The etiology at the present time is completely unknown

CLINICAL MATERIAL

In order to establish the clinical and pathologic picture of this disease a long term study involving a substantial number of patients was undertaken This study covered a period of approximately fourteen years Of the 150 cases studied, 25 were localized scleroderma There were 108 females

onset The youngest patient was

per cent of our cases developed between the ages of twenty and fifty with little difference in numbers between the three decades

This is apparently largely a disease of white-skinned people There were three Negroes in 150 patients

Neither in our own series nor in the literature have we been able to trace a single instance of the disease occurring in any other member of a family or, as far as we could learn, in any other generation All children of any of our patients with scleroderma were normal.

The duration varied tremendously One patient died eight months after the onset of the disease One patient is still living who has had scleroderma for twenty-five years

SYMPTOMS

The earliest symptoms are usually swelling and stiffness of the skin and hands Pain in the joints is almost always present and may precede any

* From the Peripheral Vascular Division, Department of Medicine and the Department of Pathology the Post Graduate Medical School and University Hospital of the New York University-Bellevue Medical Center

apparent skin changes so that arthritis is not an uncommon diagnosis in the early phase of this disease Loss of weight, weakness, and fatigue soon follow in the generalized cases. Bronze pigmentation of the skin may be pronounced. Headache is a common complaint and is not confined to any particular area Cough is not uncommon. Palpitation and dyspnea on exertion are late complaints and indicate cardiac involvement

Ulcers may be seen as small punched-out areas, usually at the extreme tip of the finger or close to the nail Paronychia is a common complication Ulcerations over the joints commonly contain small deposits of calcium which form the center of the ulcer. Where the ulcer has healed, a depressed scar may be present The most common sites are over the phalangeal joints and the elbows Where sclerodactylia is present, the fingers are shortened and rounded and the nails are much decreased in size In these cases roentgenographic visualization reveals the disappearance of the terminal tufts Occasionally the entire distal phalanx is absent.

Raynaud's syndrome may precede, occur concurrently, or follow the onset of this disease Most of these patients are sensitive to cold

LABORATORY FINDINGS

The laboratory findings as a whole do not present a true picture of the disease but merely the extent of involvement. For example, the blood chemistry may reflect the sequelae, so that if the patient has a glomerulonephritis the laboratory findings would be consistent with such a disease All other examinations follow the same pattern so that there are no laboratory tests which may be said to be conclusive or typical of scleroderma

PATHOLOGY

Since histologic examination in one of our fatal cases revealed evidence of vascular ... encephalo-
graphic tra...
showed de...
and seventeen were reported as normal. The abnormal tracings did not ... activity. Five

these findings certain presumptions may be made. It is possible that the abnormal tracings may indicate vascular lesions in the cortex of these patients It is also possible that alterations of an undetermined chemical nature may be responsible for such abnormal activity.

Lungs. Physical examination of the lungs may reveal nothing abnormal ... lungs may show several different ... e fibrotic strands extending to the ... xtending toward the base of the

... scleroderma were described years ago, they received scant attention until Weiss and his coworkers pointed out specific lesions of the myocardium which occurred in this disease Since then similar lesions have been reported by Bevans, Goetz, and others The symptoms associated with this syndrome are mainly dyspnea on exertion

and those referable to abnormalities in rhythm In spite of the pulmonary fibrosis dyspnea is more frequently symptomatic of cardiac than pulmonary involvement. It is difficult in the presence of extensive pulmonary fibrosis to calculate the relative role of these lesions since the two are commonly involved concurrently. However, the onset of dyspnea may be considered of grave prognostic importance Examination of the heart is not definitive Murmurs and abnormalities of rhythm suggestive of rheumatic heart disease

...ted as a con-

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the Q-T

...roughout

the tracing, with axis deviation and slight intraventricular conduction defects, are commonly seen

The postmortem examination of the heart frequently reveals more pathologic change than had been anticipated in the light of the examination of the heart itself prior to death This is particularly true as regards the lack of change in the electrocardiogram We have found extensive changes in the myocardium where the electrocardiogram had been normal There are few patients with this disease who do not present signs of cardiac failure

fibers were infiltrated with vascular connective tissue A third type of lesion was probably a later stage of the second, namely, an extension of the fibrosis from pericardium to endocardium.

As has been noted previously these lesions were apparently independent

vascular symptoms.

Kidneys In the clinical picture of scleroderma there is little in the disease to call attention to the kidneys unless, or until, a terminal phase is reached It has been reported that red blood cells in the urine are seen early in this disease We have not been able to confirm this finding In fact, urinalysis, kidney function tests, Addis count, etc, are all normal until the kidneys are so affected as to produce clinical signs of renal failure Once this occurs the confirmatory evidence of the laboratory becomes overwhelming and the disease becomes very rapidly fatal The literature, while reporting evidence of renal lesions, has not emphasized the fact that involvement of the kidney occurs in practically all cases where death is due to this disease.

In all of the patients autopsied, changes were found in the kidney. In 60 per cent of the known dead where necropsies were not obtained, some clinical evidence of cardiorenal failure could be obtained. In the clinical picture of the terminal phase where the kidneys are involved, protein, red blood cells and casts are found in the urine. Retention of nitrogen in the blood and occasionally lowering of the total blood protein with reversal of

the albumin globulin ratio may be seen. The blood pressure, which has hitherto been normal or below normal, becomes elevated. With these findings the associated changes in the fundi also appear.

Esophagus Ehrmann of Vienna in 1903 first described progressive dysphagia and involvement of the esophagus in a case of scleroderma. The symptoms are due mainly to a lack of motility throughout the gastro-intestinal tract. The loss of smooth muscle is the pathologic basis for the production of these symptoms throughout the gastro-intestinal tract. Analysis of the gastric contents reveals no abnormalities since the secretory or epithelial portions are not primarily affected.

Roentgenologic studies of the esophagus reveal three features which may be present individually or together: (*a*) constriction, which is usually present in the lower third of the esophagus, (*b*) lack of motility, evidenced by an increase in the time interval for the passage of food or barium from the mouth to the stomach. The greatest delay in passage is noted at the cardia Normal peristaltic movement may be absent altogether. There may be gaping and a tendency for the barium meal to adhere to the walls of the esophagus (*c*) Dilatation of the esophagus may be present with some retardation of the passage at the cardia without complete obstruction

Stomach There have been no lesions previously reported in the stomach We had one patient who had atrophy of the muscle layers of the stomach, found at autopsy

Small Intestine Kraus, in 1924, was apparently the first to report changes

There is marked delay in emptying time of the loops involved No changes of the mucosal pattern were noted

Colon Examination of the large bowel by means of barium enema shows the barium to move more slowly than usual from the rectum to the splenic flexure The colon may show areas of rigidity and peculiar narrowing with areas of sacculation There may be tendency toward sacculation without rigidity. Intestinal obstruction may be the final result of these pathologic changes

Blood Vessels All three layers of the blood vessels are affected The intima becomes greatly thickened so that even though necrosis of the muscularis may be present, the hypertrophied intima dominates the picture Complete occlusion of the lumen of the vessel by extensive proliferation of the elastica may occur The smaller arteries are chiefly affected Of the larger arteries, those chiefly affected are the digital, coronary, and cerebral arteries

DIFFERENTIATION FROM ADDISON'S DISEASE

In the past there have been occasional instances reported of the difficulty in the clinical differentiation of Addison's disease and certain forms or types of scleroderma. This difficulty is even more pronounced where the muscles are prominently affected The similarity of pigmentation of the skin, weakness, malaise and gastro-intestinal disturbance is very great While the two diseases may appear to coexist, the incidence is very uncommon. Talbott in reviewing the association of scleroderma with Addison's disease found only one case In our series the patients who presented the

greatest possibility for this diagnosis also showed no changes in the adrenal glands at autopsy.

PROGNOSIS

The course of the disease cannot be said to follow any particular pattern for all cases except where the outcome is fatal. The picture that the patient presents when first seen by the physician, whether the lesion be localized or generalized, may remain unaltered during life Complete resolution is rarely seen in the generalized type, and when it is, it is questionable whether the diagnosis of scleroderma was correct. Where the disease progresses the complaints become indicative of visceral involvement and the various physical findings and laboratory examinations confirm the subjective symptoms These findings on roentgenologic examination may be present in the absence of physical findings and may become known through routine examination On the other hand, postmortem examination may reveal extensive pathology in the absence of clinical findings. Death is usually due to a terminal bronchopneumonia complicating cardiac failure with renal insufficiency

TREATMENT

The treatment of this disease has been completely unsatisfactory We have tried every reported "cure," such as vitamins D and E, and Hytakerol We have observed patients in this series who have undergone surgical treatment such as parathyroidectomy, sympathectomy, and the like We believe that those patients reported as cured were arrested cases whose course, happily or unhappily, coincided with the therapy administered at the time We have barely avoided this pitfall on more than one occasion The vagaries of the course of this disease make any evaluation of treatment difficult. The circumscribed type apparently affords a more receptive field, according to reports of other investigators We have had little success with this type, either

DISCUSSION

HARRY KEIL

Such entities as systemic lupus erythematosus, diffuse progressive scleroderma and dermatomyositis are not truly rare diseases Their incidence has risen sharply in the past two decades, with better recognition and differentiation of the clinical pictures The recent tendency has been to throw these diseases into one category, along with a number of other entities Such embracing concepts as diffuse vascular disease, collagen diseases, mesenchymal diseases, hypersensitiveness in general and hyperglobulinemia in particular, represent useful and praiseworthy attempts to establish relationships among diseases of unknown cause on the basis of broad or more narrow similarities in pathogenesis

The d[illegible] to become [illegible] eria for the [illegible] These distinctions are important if only to determine the important question of prognosis as it concerns the patient, the family and the physician Accurate

clinical diagnosis will also be most helpful to the pathologist in assembling a uniform collection of cases for intensive study at postmortem, and, in *some respects at least, progress in this field* will be roughly proportionate to such clinicopathologic correlations

Although systemic lupus erythematosus, diffuse *progressive scleroderma* and dermatomyositis may resemble one another at certain stages, this has only happened infrequently in my observations More often the precise diagnosis has not been recognized, even when the case was typical, and there are recorded examples which illustrate this point well. Under the term scleroderma, for example, dermatologists have long recorded two types: *the circumscribed and the diffuse. The circumscribed form is often* called morphea, but it should be recognized that this is a heterogeneous concept and that occasionally morphea may occur in more widespread fashion over the skin of the body. In any event, these variants of so-called scleroderma should be discarded in any consideration of the diseases under discussion here. In this study only the affection answering to diffuse progressive scleroderma should be retained. The term acrosclerosis refers to a type of diffuse progressive scleroderma in which the major seat of changes is for the moment in the acral or distal parts of the limbs.

The early manifestations of diffuse progressive scleroderma may be conveniently classified, with transitions, under the following headings In *the first group, the signs and symptoms resemble Raynaud's disease In* other patients, the affection starts with "articular disease" in the sense that pains, swellings, discomfort, or impaired mobility may be localized in or about the larger and smaller joints In a third but small group, the first manifestations occur in the skin in parts other than the acral areas. Rarely, involvement of the esophagus or the oral mucous membrane may be a *relatively early sign.*

Although the Raynaud-like symptoms point toward vascular involvement, the fundamental disturbance in this disease seems to concern the behavior of collagen bundles Indeed, the clinical diagnostic features in diffuse progressive scleroderma are essentially secondary to the shrinkage of collagen, for example, the contractures of the fingers, the absorption of the tips of the terminal phalanges, the sclerodermic facial mask with the characteristic pointed or beaked nose showing the outlines of underlying cartilage, and the striking furrows about the lips. The esophageal changes appear also to belong in this category In my opinion the occurrence of absorption of the terminal phalanges in Raynaud's disease indicates that *the patient already has diffuse progressive scleroderma,* provided that the contours of the fingers are fairly well preserved Calcification in the soft parts of the fingers in association with this combination of features makes the diagnosis of diffuse progressive scleroderma even more secure

Whereas the collagen changes have been stressed here, this does not necessarily imply an etiologic or even a close relationship between diffuse progressive scleroderma and systemic lupus erythematosus, such as has been adduced by some observers Indeed, there is reason to believe that [illegible] ...nt, even though every once in [illegible] in a clinical sense Nor do I [illegible] ,es described in the spleen in systemic lupus erythematosus, apart from the question of specificity, war-

rants the conclusion that this points to a relationship between syste
lupus erythematosus and diffuse progressive scleroderma

Dysphagia is a symptom commonly recorded in the three diseases und consideration I would like to stress at this point the necessity for mo accurate clinical descriptions of this phenomenon because difficulty i swallowing may mean little or a great deal from a diagnostic point o view The patient with diffuse progressive scleroderma will generally say that swallowing of food causes a feeling of discomfort at the lower end of the sternum or near the pit of the stomach Only in rare instances of this disease is there encountered dysphagia with regurgitation through the nose In dermatomyositis, aside from difficulty in swallowing due to the presence of oral lesions, the outstanding and often diagnostic type of dysphagia is one in which food is regurgitated through the nose This symptom may be present at one time and absent at other times, it is caused by pathologic changes in the palatal muscles The resemblance to bulbar poliomyelitis may be striking in such instances, especially when the patient also shows painless muscular paralysis of the limbs In obscure instances the eliciting of this sign may aid in establishing the diagnosis of dermatomyositis (or polymyositis) in cases lacking the characteristic eruption or having it in an incompletely developed form As stated, this type of dysphagia may be encountered occasionally in diffuse progressive scleroderma, and the probable explanation is that the small muscles in the palate have become secondarily affected owing to the constricting effect of sclerodermatous connective tissue In systemic lupus erythematosus the only type of dysphagia I have seen has been that secondary to the presence of oral lesions Some observers have stated that dysphagia may occur in this disease owing to fibrinoid changes in the mediastinum This is an interesting possibility which remains to be confirmed in its clinical relations.

Likewise, the clinical features shown by the cutaneous lesions, including nodules, need more accurate appraisal of their diagnostic value For example, it is not enough to say that the patient had telangiectasis, diffuse progressive scleroderma often shows a type of telangiectasia occurring on the face and upper limbs in the form of small, roughly quadrangular areas, which seem to be characteristic of this disease At least, I have not seen this manifestation as yet in any other disease

I agree with Leinwand and his coworkers that "red cells in the urine are a late finding and may indicate renal involvement which is soon clinically substantiated." My coworkers and I are in the process of reviewing about a dozen cases of diffuse progressive scleroderma that came to postmortem examination and we hope to complete the project in the near future, at which time more consideration will be given to the status of the visceral lesions in this disease

In conclusion I should like to plead once more that these diseases be approached clinically as well as pathologically and by other means It is merely compounding confusion to add to the concept of diffuse progressive scleroderma such independent entities as the so-called scleroderma amyloidosum, scleredema of Buschke, Werner's disease and many other affections in which the common denominator is some degree of apparent hardness in the skin and underlying tissues

PATHOLOGY OF RHEUMATIC DISEASES

SYNOVIAL MEMBRANE IN OSTEOARTHRITIS*

RALPH K. GHORMLEY AND J. GORDON BATEMAN

In discussing the pathology of osteoarthritis, Pemberton[1] stated that "the synovial membrane may also appear normal, in marked contrast to the proliferation although there are exceptions to this, especially at the periphery." Nichols and Richardson[2] stated that "the changes in the synovial membrane and joints of this degenerative type are always secondary to the primary degeneration of the joint cartilage. Often where the cartilaginous lesion is not far advanced, and especially in small joints, there may be no apparent change in the synovial membrane, but generally where the joint lesion is extensive, and notably in the larger joints, marked changes in the synovial membrane do occur. In such cases where chronic traumatism constantly exists, the infiltration of the capsule and of the synovial tags with lymphoid and plasma cells may be extensive."

Allison and Ghormley[3] stated that "for a considerable period no obvious changes may be seen in the synovial membrane, but eventually the portion of the membrane nearest the articular margin becomes more villous. There is a hyperplasia of all its elements with occasional areas of small cell infiltrations, but the latter are rare compared with the proliferative type, in which they are a prominent feature. Newly formed blood vessels are conspicuous, and show no evidence of arteriosclerosis at this stage. Arteriosclerotic changes may now be seen in certain of the vessels of the synovial membrane, yet it is clear that these vascular changes advance with the changes in the membrane."

Bennett, Waine and Bauer[4] noted that "changes in the synovial membrane were prominent only in specimens from the sixth, seventh and eighth decades."

MATERIAL

Our study of synovial membranes in osteoarthritis has been made with material removed from hip joints at operations of various types for painful hips of adult life. The past ten years have seen an increased amount of surgical treatment of patients with such conditions. The introduction of the mold arthroplasty by Smith-Petersen[5] has developed an increased interest in the use of this surgical procedure. Previously, arthrodesis, drilling operations and acetabuloplasty had been performed in a limited number of cases. A sufficient number of patients have by this time been operated on and sufficient material has been collected to make a study of the material of interest now.

The actual material studied is from 168 patients. In order to obtain it, records of all patients seen at the Mayo Clinic over a period of five years were tabulated. From these data the patients from whom tissue, including synovial separated, and of these the patients undergoing operation were

* Abridgment of portion of thesis submitted by Dr. Bateman to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Orthopedic Surgery.

membrane, was removed, were selected. Specimens of synovial membrane had not been taken in every case. The reason for this may be interpreted in two ways. (*a*) No significant synovial changes were noted at the time of the operation, or (*b*) the surgeon did not remove any synovial membrane

METHOD

It is our distinct impression that in many cases of osteoarthritis of the hip joint, very little change in the synovial membrane is found at operation On the other hand, changes in the synovial membrane may be marked In fact, at times the synovitis is as marked as that occasionally seen in cases of rheumatoid arthritis



Fig 80 Normal synovial membrane showing normal number and size of capillaries (Hematoxylin and eosin, ×120)

In reviewing these cases, we noted the diagnosis as "osteoarthritis," or osteoarthritis secondary to some other condition such as Legg-Perthes' disease, old slipped epiphysis or the like For years we have attempted to designate the primary condition in osteoarthritis of the hip which has come under our observation On the basis of our study of synovial changes it seemed unlikely that, except in certain types, the primary condition will have much effect on the development of changes in the synovial membrane

In cases of osteochondromatosis, old septic arthritis and old rheumatoid arthritis and spondylitis there are of course significant changes in the primary joint condition which in some instances may carry over into the osteoarthritic stage of the disease and cause a mixed type of synovial change to appear.

Because of previous reference to various types of synovial change, the following changes have been looked for and, if found, have been noted subsynovial fibrosis, increased capillary vascularity, increased capillary engorgement, pericapillary fibrosis, medial fibrosis of arteries, diffuse in-

filtration, focal collections, recent hemorrhage, increased number of villi, marked edema, necrosis, calcium spicules, fatty metamorphosis, giant cells and deposits of hemosiderin.

FINDINGS

As a control group, synovial membranes from patients for whom amputations had been performed for various reasons were studied (Fig. 80). Changes in the pathologic synovial membranes were looked for, and some were found in a small number of cases. In brief, it may be stated that such changes as increase in subsynovial fibrosis, increase in the number of subsynovial vessels, pericapillary fibrosis, capillary engorgement and medial fibrosis of arteries may be found in persons of the upper age groups fairly consistently, indicating that to a certain extent such changes represent degenerative changes accompanying advancing years.

In our study, sections of synovial membrane were obtained and studied in 168 cases. Of these, 17 cases were excluded from the series because of inadequate clinical data or pathologic material, and 27 cases were excluded because the conditions could not be considered to be osteoarthritis of the hip. Table 43 indicates the diagnosis in the remaining 124 cases.

Table 43. Diagnosis in 124 Cases of Osteoarthritis of the Hip

CONDITION	CASES
Osteoarthritis, no cause apparent	36
Old slipped capital femoral epiphysis	15
Aseptic necrosis of head of femur	14
Traumatic arthritis	12
Congenital dysplasia of the hip	12
Old septic arthritis	8
Old Legg-Perthes' disease	7
Old rheumatoid arthritis	7
Osteochondritis dissecans	6
Otto pelvis	4
Osteochondromatosis	3
TOTAL	124

The first group is the largest, and in some instances may represent what we occasionally see and recognize as generalized osteoarthritis. In other instances it was impossible to determine from the patient's history what, if any, antecedent condition might be regarded as having any bearing on the development of the osteoarthritis of the hip as seen at the time of our examination. Of the other groups designated, a word of explanation is necessary in one or two cases. "Old septic arthritis," in our opinion, represented instances in which septic arthritis of childhood or adolescence had left the joint surfaces so changed as to create an irritation and to favor the subsequent development of osteoarthritic changes. "Old rheumatoid arthritis" denotes instances in which obvious pre-existing rheumatoid arthritis had been present and had left a damaged and altered joint surface on which osteoarthritis had developed.

A summary of the number of studies of the various types of changes

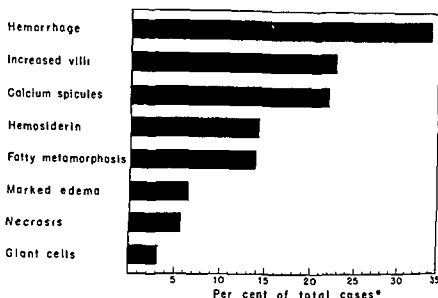


Fig 81 Incidence of some changes encountered in this series

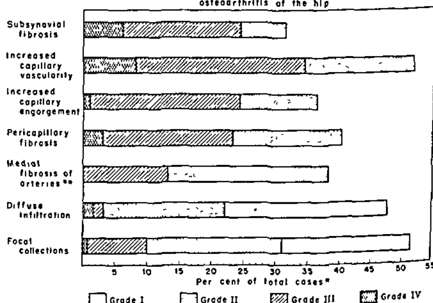


Fig 82 Incidence of other changes encountered, graded according to degree

was made, the percentages distributed in the ent…
in Figures 81 and 82 It may…
…percentage
…characteristic or diagnostic of the con-
…of the changes were present to a comparatively small degree
when tabulated according to the basis of 1 to 4, as in the case of the presence of focal collections, where the grading of these revealed the results seen in Figure 82. Figures 83 and 84 illustrate changes encountered

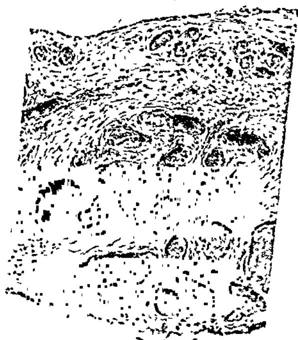


Fig 83 Synovial membrane in a case of osteoarthritis. There is marked increase in capillary vascularity and the capillaries are engorged There is no infiltration with plasma cells or lymphocytes All of the small dark cells in this section are synovial cells (Hematoxylin and eosin, ×110)

The incidence of these various changes in the various types of osteoarthritis was tabulated for each group No consistently high percentage of incidence could be noted for any group The highest percentage incidence of any one observation was 83, for diffuse infiltration noted in ten of twelve cases of osteoarthritis of the hip secondary to congenitally shallow acetabulum or dysplasia of the hip No definitely consistent correlation between the extent of the changes noted and the duration of symptoms could be made In some cases in which the condition was of short duration changes were as marked as in instances in which the condition was of longer duration.

COMMENT

In summarizing the significance of these findings, we again point out that the figures represent only a comparatively small number of the patients whose hips were operated on and from whom specimens of synovial membrane might have been saved had there been sufficient synovial change to justify the surgeon's asking for a study of the specimen. Frequently, the gross changes are so slight that no particular effort is made to obtain a specimen of the membrane



... of congenital dysplasia of the hip with hyper- ... y engorge- ... is A focal ... ise infiltra- ... is (Hema-

The obvious conclusion to be drawn is that there is no consistently typical pathologic picture of the synovial membrane in osteoarthritis In some instances the changes in the synovial membrane are marked enough to make one suspect a mixed type of arthritis, such as osteoarthritis and rheumatoid arthritis In many instances this is hard to prove, although in some of our cases ... had developed in a l...

Wl... ques- tion. ... aking- down or degeneration of the cartilaginous surfaces and, to a lesser extent, of the bone, must in some cases excite a reaction in the synovial mem-

brane which leads to the changes noted, but to a variable degree In some cases advanced osteoarthritic changes may be present without much in the way of synovial change In some cases the changes result from a mixed type of arthritic involvement of the joint

From a practical standpoint it should be noted that we frequently see, particularly in cases in which the head of the femur is greatly enlarged, marked adhesions of the synovial membrane and capsule to the head of the femur These may be postulated as being a cause of pain in such joints In other cases, however, adhesions of the membrane to the head were not noted, and cannot therefore be said to be the more common cause of pain in these joints.

Our work may be said, therefore, to substantiate the earlier work of such writers as Nichols and Richardson, Pemberton and others Changes in the synovial membrane are not the characteristic pathologic changes in osteoarthritis, but are secondary to the other joint changes, particularly of cartilage and bone

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3 [illegible]

4 [illegible]

5 [illegible]

DISCUSSION

HUBERT J GIBSON

My experience of osteoarthritic synovial material is in agreement with that of Drs Ghormley and Bateman The reaction is mainly one of fibrosis and degeneration and it differs markedly from that of rheumatoid arthritis

At the same time small and widely spaced paravascular lymphocytic foci in the fibrous tissue suggest that in diagnosis regard must be had to quantitative as well as qualitative standards This important question of quantity of reaction has been repeatedly raised by both old and new work on the rheumatic diseases Bennett, Waine and Bauer[1] showed that clinical osteoarthritis is probably a quantitative increase of the changes due to stress, strain and ageing which are seen in all joints after the second decade In the same way Clawson and his co-workers[2] have suggested that the round cell reaction of rheumatoid muscle may be a quantitative increase of that found in nonrheumatic persons, especially in muscles such as the diaphragm and the intercostals which are subject to the continued stress of respiration

[illegible] ronic [illegible] died [illegible] cell reaction seen in muscle, nerve sheaths and elsewhere, including that seen in rheumatoid arthritis

If we accept the view that these round cell foci have no essential relationship to arthritis but are due to intercurrent mechanical or toxic injury to collagen, the question of their significance in rheumatoid arthritis arises A sequence of such sites may be drawn up commencing with normal muscle or osteoarthritic synovia and passing to rheumatoid skin, muscle and nerve, the peripheral zone of subcutaneous nodules, the epiphyseal marrow, joint capsule, subsynovial fat and finally synovial villi of rheumatoid arthritis Such a sequence extends from unrelated nonrheumatic diseases to the very center of rheumatoid arthritic activity, and the difference between each step is a difference in quantity and not quality of reaction

This conception of quantitative difference leads to a further question Is the difference between a healthy person and an osteoarthritic patient of the same age a quantitative difference in the resistance of articular cartilage to the normal microtraumata of use? This may well be the X factor of the disease. Such an abnormal lability of cartilage might be inherited,[3] but the alternative raised by recent announcements is that it may be acquired by the lack of endocrine factors which raise tissue resistance to damage as such, irrespective of the nature of the damaging agents I feel that extreme interest will attach to the influence, if any, of cortisone on the development of osteoarthritis in joints damaged by rheumatoid arthritis

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* * *

THE HISTOPATHOLOGY OF RHEUMATOID ARTHRITIS, ESPECIALLY IN THE EXTRA-ARTICULAR MANIFESTATIONS

G. D. KERSLEY AND HUBERT J. GIBSON

The first important work on the histopathology of rheumatoid disease was done in America[1-4] This work has been confirmed and amplified by
studies carried out at the F
Bath, England[5-7] Previous
arthritis have shown two r
in different situations: (*a*)
membrane, nerve trunks, scle and ski ... ous nodule,
lagenous connective tissue ypically in th
where its association with layer of pri ... ists gives a
picture which has been reg stic.
By a study of the histo r and
attempt has made to two div

clusion is reached that the fully developed rheumatoid lesion typically contains both features and that necrosis as found in subcutaneous nodules may occur in synovia and muscles, while round cell reaction is invariably present in the capsular zone of nodules

SUBCUTANEOUS NODULES

The development of subcutaneous nodules illustrates this relationship The earliest nodule examined (Fig 85) showed a patch of fibrosis in subcutaneous fat, surrounded by a ring of small lymphocytic foci From a study



Fig 85 A very early subcutaneous nodule from a case of rheumatoid arthritis It shows a localized patch of fibrosis in subcutaneous fat, surrounded by pericapillary lymphocytic accumulations No necrosis is evident at this stage

of many subcutaneous nodules the following sequence is suggested as describing its further development First, the area of fibrosis increases with the lymphocytes occupying a capsular zone of looser texture at the periphery Fibrinoid degeneration passing on to necrosis then occurs at the center (Fig 86) In the early stages the necrotic areas are seen to be elongate and tortuous when cut longitudinally The necrotic areas fuse and liquefaction then occurs, leaving as an end result a cyst with fibrous wall containing necrotic tissue debris

A similar sequence can be observed in other situations

SYNOVIAL MEMBRANE

Fibrosis occurs in the membrane and subsynovial fat with round cell reaction, plasma cells and later lymphocytes predominating

Necrosis then occurs, typically in the form of fissuring of the fibrotic membrane along lines of cleavage from the surface (Fig 87) Such lines



Fig 86 A section through a rheumatoid nodule which shows necrosis leading to cavity formation



Fig 87 Synovial membrane in rheumatoid arthritis, showing necrosis in the form of fissuring of the thickened fibrotic membrane A palisade of radially arranged fibroblasts appears around part of the fissure

meet and branch, giving rise to villous processes and later detached fragments. A palisade of fibroblasts is seen along the lines of linear necrosis and the appearance is very similar to that of the subcutaneous nodule, modified by the fact that the process is occurring in relation to a cavity and not a solid mass (Fig 88). Superficial necrosis of the surface layer and of the villi then occurs and the necrotic tissue is exfoliated into the joint cavity.



Fig 88 Synovial membrane in rheumatoid arthritis, showing a patch of necrosis surrounded by a well marked palisade The appearance is identical with that of a subcutaneous nodule

The end result is again a fibrous cyst with round cell foci in the wall and products of tissue degeneration in the lumen

LESIONS IN MUSCLE TISSUE

Round cell reaction is the predominant feature in this situation Necrosis is rare It has, however, been found at postmortem in an intercostal muscle in which a fibrous sac containing necrotic debris was found (Fig 89). Microscopically the appearances were strikingly like those seen in excavated nodules and in synovia

LESIONS IN NERVE TISSUE

Again lymphocytes predominate, but Freund et al[3] have described a center acellular homogeneous zone containing collagen strands but without fibrin.

RHEUMATOID TENOSYNOVITIS AND BURSITIS

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They are forms of extra-articular rheumatoid synovitis In all situations the lesions are inflammatory as shown by lymphocytic reaction, and degenerative as shown in necrosis The end result at each site appears to be a fibrous walled cyst containing the products of tissue degeneration



Fig 89 Intercostal muscle from an advanced case of rheumatoid arthritis, showing a large necrotic lesion It is encapsulated by dense fibrous tissue and contains tissue debris, including much cholesterol

COMMENT

The widespread nature of the lesions which affect all the mesodermal tissues has been demonstrated Collections of round cells, namely, lymphocytes and plasma cells, proliferation and degeneration in all the coats of the smaller blood vessels, and swelling, fibrinoid degeneration, necrosis and proliferation of collagenous fibers in the connective tissues have been shown to occur in the skeletal muscles, heart, pericardium, around nerves, in the synovia and capsules of joints, in cancellous bone, in adipose tissue and in the skin.

In small random samples of muscle taken by biopsy, each smaller than a postage stamp, the above mentioned changes were found in 64 per cent of *seventy rheumatoid cases They were also found occasionally*, but much more rarely, in other rheumatic conditions and controls (see Table 44). They have been seen in muscle taken from a case of Volkmann's contracture, in a reaction to a foreign body in the breast, and in a case of post-traumatic myositis

In the rheumatoid cases the frequency of occurrence did not vary with the activity of the disease, the degree of muscle wasting, the proximity to an affected joint, or the previous administration of gold therapy Its frequency did, however, increase with the duration of the disease.

In a consecutive series of fifty autopsies on nonrheumatic cases, muscle

was removed for examination from seven sites in each case. The amount of tissue examined was approximately twice that usually obtained on biopsy On sectioning this tissue, fields were found which resembled those seen in rheumatoid disease in about 9 per cent, as compared with 64 per cent

Table 44. Number of Positive Findings on Muscle Biopsy in Various Rheumatic Syndromes

SYNDROME	NUMBER OF CASES	NUMBER POSITIVE
Rheumatoid disease	70	45
Rheumatoid spondylitis	17	1
Gonococcal arthritis	7	0
Still's disease	3	1
Psoriatic arthritis	4	1
Osteoarthritis	8	1
Gout	6	0

using half the quantity of tissue in rheumatoid arthritis Positive results were found, according to the site chosen, in 16 per cent in diaphragmatic muscle, 9 per cent deltoid, 8 per cent pectoralis major, 7 per cent sternomastoid, 5 per cent psoas and in no case in the heart muscle.

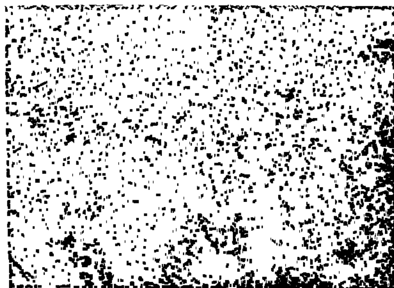


FIG. 90 A section from a nodule from a case intermediate between rheumatic fever and rheumatoid arthritis

Nodule formation has been examined and the symmetry of the arrangement of the palisade layer and the central necrosis makes this the most

then progressed to typical rheumatoid deformity, a nodule was excised

which also showed a histology intermediate between that of rheumatoid disease and rheumatic fever (Fig 90).

... was excised from the calf of a patient with otherwise typical rheumatoid symptoms. This sac contained a *creamy deposit* consisting largely of cholesterol (Fig. 91).

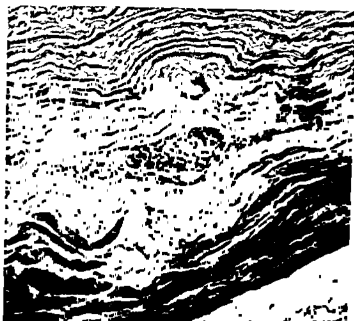


Fig 91. A section through the wall of a bursa containing cholesterol, removed from the calf of a patient with rheumatoid arthritis

Again degeneration in muscle and tendon may be the cause of spontaneous ruptures which may occur in a number of sites in the same patient They have been seen in a patient in whom the disease was only moderately active and not in a very advanced stage as judged by joint deformities and general condition

To summarize, it is felt that the histologic changes in rheumatoid disease are not specific though they are seen much more commonly in this condition than in any other They become more widespread the longer the duration of the disease and it is thought that they would always be found if sufficient tissue were available for examination They are probably a nonspecific biochemical reaction of connective tissue which may be set in train by a number of different stimuli

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* * *

THE DIAGNOSTIC VALUE OF SYNOVIAL FLUID FINDINGS

MARIAN W. ROPES

The available anatomic and physiologic evidence indicates that the joint cavity is a large tissue space and synovial fluid is tissue fluid As would be expected from this hypothesis, synovial fluid reflects changes produced by disease in synovial tissues The alterations in the fluid vary with the type, duration and severity of tissue inflammation and, therefore, are often of value in diagnosis

Aspiration is simple and safe The only condition in which it may be dangerous is hemophilic arthritis, and even in this disease aspiration can be done safely if the clotting time is brought to normal before tapping

Aspiration is indicated in essentially all cases of joint disease in which the diagnosis is in question. Furthermore, it is of aid in determining the prognosis in infectious arthritis As soon as fluid recurs in an infected joint (every one to two days), aspiration is of value both therapeutically, to drain the joint, and prognostically, to determine whether whatever treatment is being used is adequate as indicated by improvement in the fluid findings.

The most frequent use and the greatest value of aspiration are in diagnosis, and depend on the fact that the changes in synovial fluid increase with increasing severity of tissue inflammation

CORRELATION BETWEEN CHANGES IN FLUID AND SEVERITY OF INFLAMMATION

In the mildest inflammation, that due to trauma (as in traumatic arthritis, degenerative joint disease and Charcot's joints), there usually is little change from normal and the fluid alterations are never marked

In mild cases of infectious arthritis or mild cases of rheumatoid arthritis, the changes in the fluid are still slight With increasing severity of disease the alterations in the fluid increase, though the degree of change is not directly proportional to the severity This increase with severity is well demonstrated in gonococcal arthritis, in which the severe cases with positive cultures in the joint fluid show much greater changes than the cases with negative cultures in the fluid A positive culture has never been obtained in a fluid with a leukocyte count of less than 30,000 Total leukocyte and polymorphonuclear cell counts and the sugar concentration show the greatest differences In rheumatoid arthritis it is *not usually the* cell count that indicates the degree of severity However, an average sugar level of 55 mg per 100 cc and a globulin content of 4.1 gm per 100 cc

were found in severe cases, in contrast to a sugar concentration of 81 mg per 100 cc and globulin content of 2.9 gm per 100 cc in mild cases.

In intermittent effusions of short duration the changes in the fluid, reflecting variations in severity of tissue inflammation, occur rapidly and can be followed if fluid is aspirated daily, as in the case of one patient who had generalized rheumatoid arthritis with bilateral knee involvement The effusions in the knees recurred with precise regularity with intervals of six days between the peaks of the effusions. As the effusions appeared the leukocyte counts rose to 22,000 and 31,000 in the two joints, and the sugar levels fell to 74 and 50 mg per 100 cc. With subsidence of the effusions the counts fell to 6600 and 5000, and the sugar concentrations rose to 103 and 103 mg. per 100 cc.

Similar changes in fluid findings as the severity of joint inflammation decreased were found in other cases of rheumatoid arthritis and in cases of rheumatic fever and infectious arthritis. The total leukocyte and polymorphonuclear counts fell as the joint disease subsided and the effusions disappeared.

DIAGNOSTIC DIFFERENCES IN FLUIDS

Analysis of the findings in 1000 synovial effusions indicated that joint fluids could be divided into two groups on the basis of the degree of change

Table 45. Cytological Findings in Synovial Fluids

	FLUID		APPEARANCE	CLOT	LEUKOCYTES per cu mm	POLYS per cent
	NORMAL	min	CLEAR	0	13	0
		av	"	"	63	65
		max	"	"	180	25
GROUP I	TRAUMATIC		CLEAR	0	200	0
			"		1500	10
			"	++	5,300	30
	CHARCOT		CLEAR	0	10	0
					519	17
			TURBID (RED)	±	1,900	45
	DEGENERATIVE		CLEAR	0	70	0
					521	8
			"	++	1,930	58
	RHEUMATIC FEVER		SLIGHTLY TURBID	0	1000	8
					10,400	46
				+++	63,000	98
	GOUT		TURBID	±	1000	48
			"		13,800	83
			"	++	31,400	94
GROUP II	RHEUMATOID		CLEAR	0	600	5
					14,000	65
			TURBID	+++	66,000	96
	TUBERCULOUS		TURBID	0	2,500	29
			"		23,500	67
			"	++	105,000	96
	GONOCOCCAL		TURBID	0	1,500	2
			"		14,000	65
			"	+++	108,000	96
	SEPTIC		VERY TURBID	++	25600	75
					65,400	95
				+++	213,000	100

in the fluids. Group I, in which there are only relatively slight changes from normal, was found to include all diseases in which the inflammation is due to trauma The most common diseases in this group are those shown in Table 45—traumatic arthritis, degenerative joint disease and *Charcot's* joints. Group II includes all types of infectious arthritis and rheumatoid

arthritis. Septic arthritis here includes *B. coli*, pneumococcal, streptococcal and staphylococcal infections. Fluids from patients with rheumatic fever, which are listed separately, resemble those of group I in many respects but the abnormalities in cell counts are greater than those of group I. Gouty fluids resemble group II fluids in general but the changes are somewhat less marked.

The differences between the two groups of fluid are of value in diagnosis In Table 45 the findings in normal fluids are given at the top for comparison It can be seen that none of the changes in group I fluids are great Some of the important differences between the groups are apparent merely on observation of the fluid or with simple tests

Clarity and Clotting Tendency Normal fluid is clear and does not clot Group I fluids are usually clear (unless bloody, as they often are in Charcot's joints) The fluids of this group usually do not clot, or if they do, the clots formed are small and friable Group II fluids, on the other hand, are usually turbid However, here, as in all fluid findings, there may be great variation in rheumatoid arthritis and fluid from mild cases may be clear, though the majority of rheumatoid fluids are turbid The fluids of group II frequently clot and often form large, firm clots, especially in infectious arthritis

Cell Counts The differences between the groups are marked in the cell counts The average leukocyte count in normal fluid is 63 In group I fluids there is a slight increase in cells but the average remains low, 500 to 1500, and the highest count we have seen in this group is 5300 Similarly, the

counts are much higher than in group I fluids, though in all other respects the fluids are comparable Group II fluids show a much greater increase in cell counts with averages of 14,000 in rheumatoid arthritis and as high as 65,400 in septic arthritis The latter figure does not include some fluids that were thick pus on which accurate cell counts could not be done The average polymorphonuclear percentage also rises markedly in group II fluids, to 65 in rheumatoid, tuberculous and gonococcal arthritis and to

Protein Concentrations Some of the relatively simple chemical tests furnish other differences between the two groups (Table 46) The average protein concent[illegible]

is an increa[illegible]

the highest

increase is in the globulin fraction, from the normal average of 05 gm. to averages of 0 8 to 1 1 gm per 100 cc In group II fluids, on the other hand,

fluids

Alterations in the concentrations of the various protein fractions as dem-

onstrated in the electrophoretic patterns of synovial fluids also aid in differentiating the two groups of joint diseases In traumatic fluids differential permeability to individual protein fractions is found The concentration of albumin is higher in the fluid than in the serum, the alpha-1 globulin concentration is essentially the same, and the alpha-2 and gamma globulin concentrations are lower in the fluid. In early or mild cases of rheumatoid arthritis, the electrophoretic patterns in the fluids usually resembled those of traumatic fluids In the majority of fluids from rheumatoid arthritis, however, the albumin concentration in the fluid was equal to or lower than that in the serum and the gamma globulin in the fluid was higher In many

Table 46 Clinical Findings in Synovial Fluids

	FLUID	VISCOSITY			PROTEIN GM/100 CC			GLOBULIN GM/100 CC			MUCIN GM/100 CC			SUGAR DIFF MG/100 CC		
		MIN	AV	MAX	MIN	AV	MAX	MIN	AV	MAX	MIN	AV	MAX	MIN	AV	MAX
	NORMAL	51	150	403	1 3	1 7	2 1		0 05*		0 55	0 85	1 10	<10	<10	<10
GROUP I	TRAUMATIC	15	37	54	3 2	4 0	5 1	0 7	0 8	1 4	0 35	0 73	1 57	0	7	20
GROUP I	CHARCOT	32	99	228	1 6	3 3	5 1	0 3	1 1	1 7	0 07	0 59	1 61	0	10	19
GROUP I	DEGENERATIVE	4	88	343	1 8	3 2	4 9	0 3	0 8	1 4	0 23	0 67	1 03	6	6	6
	RHEUMATIC FEVER	31	38	50	1 6	3 5	4 9	0 4	0 7	1 1	0 64	0 87	1 21	6	6	6
	GOUT	4	5	6	3 1	4 3	5 0	1 1	1 4	1 8	0 28	0 53	0 80	0	12	41
GROUP II	RHEUMATOID	4	12	66	3 0	4 9	8 9	1 2	2 2	6 8	TRACE	0 52	1 35	0	31	88
GROUP II	TUBERCULOUS		13*		4 1	5 1	6 1		1 4*		0 41	0 62	1 19	0	57	108
GROUP II	GONOCOCCAL	3	11	21	4 3	5 4	6 9	1 3	2 1	3 1	0 13	0 49	1 29	0	26	97
GROUP II	SEPTIC	25	33	38	3 7	5 0	6 9	1 4	1 9	2 2	TRACE	0 40	0 58	40	71	122

patients with rheumatoid arthritis, the serum albumin is very low and the gamma globulin markedly elevated and the fluid reflects these changes with apparently very little differential permeability for individual protein fractions There is apparently a tendency for the gamma globulin in the fluid to increase in effusions of long duration. In rheumatic fever the electrophoretic pattern, like the majority of the other fluid findings in this disease, resembles that of traumatic fluids The albumin concentration is higher and the gamma globulin concentration lower in the fluid than in the serum

Sugar Concentrations The sugar concentrations also aid in differentiating the two groups In Table 46 are shown differences between the serum sugar and the fluid sugar Normally, the difference is less than 10 mg. per [illegible] the difference remains [illegible] he difference increases [illegible] per 100 cc The high figures represent, of course, fluids with very low or zero sugar levels Such

levels are found not only in tuberculous and other types of infectious ar-

precipitate obtained with acetic acid The concentration does decrease from the average normal of 85 gm per 100 cc to 0 6 to 0 7 gm. in group I fluids and 0 4 to 0 6 gm in group II fluids, but the change in viscosity is more reliable The average normal viscosity is 150, in contrast to 37 to 99 in group I fluids and 12 to 33 in group II fluids The best differentiation comes from a comparison of the precipitates obtained by adding acetic acid to the joint fluid to a final concentration of 1 per cent The precipitate from normal fluid is a tough, ropey clump with clear surrounding solution In group I fluids the precipitate remains ropey though sometimes it is less tough and can be broken up slightly with a stirring rod The solution remains practically clear In group II fluids the mucin usually precipitates in a soft clump with cloudy solution In severe cases there is no clump and only a cloudy solution is obtained.

COMMENT

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count above 5000 per cu mm , an absolute polymorphonuclear count above 1000 per cu mm , a protein concentration above 5 5 gm per 100 cc , a serum-

fluid has only slight changes from the normal, such as those found in group I fluids it does not prove that it is a traumatic fluid since fluids from mild cases of rheumatoid arthritis and even of gonococcal arthritis may show only slight changes from normal

In addition to the value in differentiating infectious and rheumatoid fluids from those of traumatic origin, the fluid findings are of some value in suggesting other differentials For instance, in our experience sixteen out of eighteen rheumatic fever fluids have had good mucin precipitates, whereas the mucin in rheumatoid fluids usually precipitates poorly Simi-

or a few months) the combination of a relatively low cell count (25,000 or below) and polymorphonuclear forms of 50 per cent or less with a low content of sugar (20 mg or below) can, we think, be found only in tuberculosis Not all cases of tuberculous arthritis show this type of fluid, as shown by the four exceptions we have encountered in twenty patients.

CASE STUDY

An eighteen-year-old white boy was admitted with a complaint of pain and swelling in the left knee of five months' duration A cyst of the internal semilunar

cartilage of the left knee had been removed twenty-one months before admission. The knee had remained absolutely symptom-free until five months before admission, when he was thrown against an anchor bar on a ship during a storm, striking the left knee. The knee had been swollen and painful since that time Examination showed effusion in the left knee with tenderness over the lateral ligament and the posterolateral aspect of the lateral meniscus The capsule was markedly thickened A diagnosis of traumatic synovitis was made and synovectomy and removal of external semilunar cartilage were performed. Fluid obtained at operation had a total cell count of 5250 with 58 per cent polymorphonuclear forms, contained no sugar and had a protein content of 5 38 gm per 100 cc., all three findings being entirely inconsistent with those of traumatic fluids and, considered together, suggesting a diagnosis of tuberculosis Frozen sections of the synovialis had not been made at operation because the diagnosis was thought definite and the examination of the fluid gave the first indication that the diagnosis was incorrect. Histologic examination of the synovialis showed tuberculosis and the knee was fused subsequently.

In this case, preoperative examination of the fluid would have suggested the correct diagnosis, which could have been confirmed by examination of frozen sections of synovialis at the first operation, and a second operation would have been unnecessary

In summary, the changes in joint fluid, which reflect the degree of severity of tissue inflammation, make fluid examination of diagnostic value The chief value is in differentiation of various types of infectious arthritis and rheumatoid arthritis from joint diseases that are traumatic in origin

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HISTOLOGIC AND CHEMICAL CHANGES IN SKELETAL MUSCLE OF PATIENTS WITH RHEUMATIC AND NONRHEUMATIC DISEASES*

JOSEPH J. BUNIM, LEON SOKOLOFF, EDWARD J. BIEN, SIGMUND L. WILENS, MORRIS ZIFF AND CURRIER MCEWEN

Freund, Steiner and associates[1, 2] have reported the presence of an inflammatory lesion in the skeletal muscle of all patients with rheumatoid arthritis and in none of their controls They considered this muscle nodule specific for rheumatoid arthritis and recommended that muscle biopsy be done as a diagnostic aid Several workers in England[3, 4] and in this country[5]

In ses, we have stated that this lesion was that it, th ore, was not specific for rheumatoid arthritis Ogryzlo[7] reached the s usion. Klinge and Grzimek[8] described similar muscle lesions in tw of rheumatoid arthritis, they also con ese nodules no

This report presents of a combi and biochemi-

* From the Departments and Pathology Group on Rheumatic Diseases, New York U of Medici Hospital, New York City. Th by tion and t Webster-U

cal study of skeletal muscle extended to 202 cases* including 57 cases of rheumatoid arthritis, 76 other types of arthritis, 156 nonrheumatic diseases and 13 normal, apparently healthy volunteers The purpose of this investigation was two-fold: first to determine the specificity and diagnostic value of the cellular nodule, and second, to ascertain whether the histologic changes observed in a given muscle specimen were associated with alterations in certain chemical constituents of the muscle

HISTOLOGIC STUDIES

In over 90 per cent of the cases, muscle was obtained by biopsy, usually of the gastrocnemius and, wherever possible, remote from an affected joint.



Fig 92 Section of a lesion from a thirty-four-year-old Negro woman with rheumatoid arthritis, an example of the largest type of lesion seen in this series

In each instance, approximately 400 serial sections were cut and every fifth slide was stained The average size of each section was 1 sq cm and the sections were cut at 8 microns A total of more than 80,000 sections were cut and of these, 17,000 were examined In each positive biopsy, the number of nodules and the number of cells in the largest nodule were counted The mean diameter of the largest nodule was measured with an eye-piece micrometer Specified criteria for a typical muscle nodule were adopted and applied to the control and the rheumatoid cases alike These criteria, the incidence of lesions per unit volume of muscle in the rheumatic cases and nonrheumatic controls and the average size of the infiltrates in these groups, are reported and discussed in another paper[9]

In an illustration in the paper of Freund and associates,[4] the lesions are shown as fairly compact aggregates of lymphocytes with a small proportion

* The senior author examined each patient in this series and collected the laboratory data necessary to complete the diagnosis.

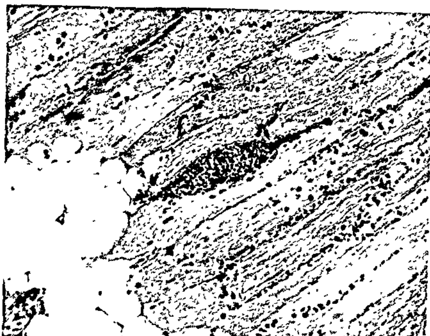


Fig 96 Section of an *endomysial* lesion from the gastrocnemius of a fifty-nine-year-old man with osteoarthritis of the spine

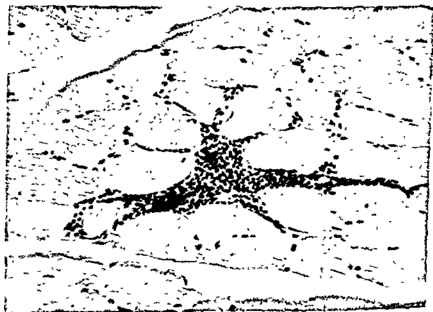


Fig 97 Section of an endomysial lesion from the gastrocnemius of an apparently healthy thirty-one-year-old man

F [illegible]
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was 7 4 mg. per cent The lesion is located in the perimysial margin of a muscle bundle and lies next to an arteriole

Figure 96 is one of four endomysial lesions in the gastrocnemius of a fifty-nine-year-old white man with osteoarthritis of the spine No other types of arthritis coexisted The largest lesion had 280 cells, principally lymphocytes, with a smaller proportion of mononuclear cells

Figure 97 is an endomysial lesion in the gastrocnemius of an apparently healthy adult volunteer He was a thirty-one-year-old white man, a hospital attendant, with no history or physical signs of any of the rheumatic

Table 47 Histological Findings in Muscles of 202 Subjects

DISEASE	TOTAL	POSITIVE	DOUBTFUL	NEGATIVE	ATYPICAL
Rheumatoid arthritis	57	32	8	17	0
Ankylosing spondylitis	10	4	2	3	1
Rheumatic fever, active	21	7	4	10	0
Rheumatic heart disease, inactive	11	0	3	8	0
Osteoarthritis	19	4	4	11	0
Joint tuberculosis	10	3	0	6	1
Pulmonary tuberculosis	6	0	1	3	2
Gout	8	3	3	2	0
Subacute bacterial endocarditis	6	4	1	1	0
Trichinosis	3	—	—	—	3
Miscellaneous*	38	8	10	18	2
Normal	13	3	3	7	0
TOTAL	202	68	39	86	9
Per cent of 57 rheumatoid cases	100	56	14	30	0
Per cent of 145 nonrheumatoid cases	100	25	21	48	6

[illegible]

diseases The electrocardiogram, erythrocyte sedimentation rate, roentgenogram of the chest, serum titer of streptococcus agglutinins, sensitized sheep red cells agglutinins[11] and trichinella antigen precipitins were normal. This nodule has more than 200 closely packed lymphocytes and is considered an acceptable lesion in every respect

The results of the histologic study are presented in Table 47. It will be noted that besides the positive and negative biopsies (by which is meant [illegible]

bercle, were classified as atypical

Fifty-six per cent of the rheumatoid cases had positive biopsies in contrast to 25 per cent of the control group Despite a thorough search, the striated muscle of at least 30 per cent of the patients with rheumatoid arthritis failed to show cellular infiltrates It is true, however, that in no

other disease was the incidence of muscle nodules as high as in rheumatoid arthritis, with the exception of subacute bacterial endocarditis. It is interesting that Marie-Strumpell spondylitis ranks close to rheumatoid arthritis, with a rating of 40 per cent. The important finding is that one-fourth of the patients with diseases other than rheumatoid arthritis presented inflammatory muscle lesions indistinguishable from those seen in rheumatoid arthritis From this observation it follows that the lesion is not specific for any one disease and, hence, is of limited diagnostic value

In the skeletal muscle of four patients with rheumatoid arthritis a vascular lesion was observed which will be described in another paper [12]

BIOCHEMICAL STUDIES

From forty subjects, approximately 4 gm of the gastrocnemius muscle was removed by biopsy under local procaine anesthesia and divided into

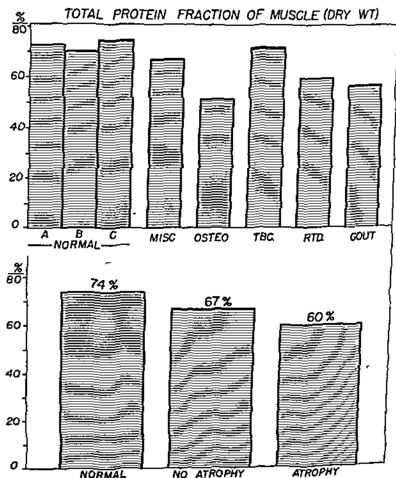


Fig 98 Comparison of the total protein fraction in dried muscle of normal subjects with that of patients with various diseases

two sections One section was fixed for histologic study and the other was refrigerated immediately and finely minced for chemical analysis Deter-

minations were made of the water content, total nitrogen, nonprotein nitrogen and protein. Further analysis was made of two components of the protein fraction, myosin and collagen. The myosin was then treated for its adenosinetriphosphatase activity when incubated with the substrate sodium adenosinetriphosphate for six minutes at 37° C The results were expressed in micrograms of phosphorus liberated per milligram of myosin

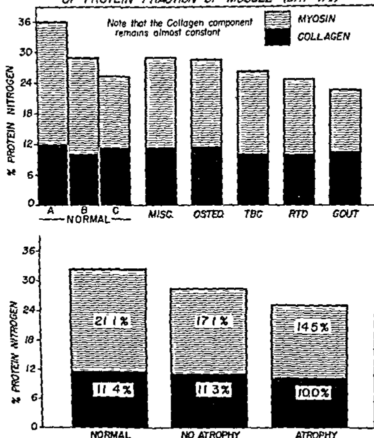


Fig 99 Comparison of the collagen and myosin fractions of dried muscle in normal subjects with those in patients with various diseases

The values obtained for these biochemical substances were then compared with the histologic changes seen in the same muscle, with particular reference to atrophy and the presence of cellular nodules. Patients with severe atrophy were not included because muscle biopsy was not feasible The details of the chemical methods employed and a full analysis of the results will be the subject of a separate report [12]

The forty subjects consisted of thirteen healthy adult males, eight patients with rheumatoid arthritis, four with gout, four with tuberculous

spondylitis, three with degenerative joint disease, two with Marie-Strumpell spondylitis, two with subacute bacterial endocarditis, and one each with syphilis, pulmonary tuberculosis, erythema nodosum and bronchial asthma

In Figures 98 to 100 the cases are grouped in two categories: One is arranged according to the clinical diagnoses—miscellaneous diseases, osteoarthritis, tuberculous arthritis, rheumatoid arthritis and gout—and the other

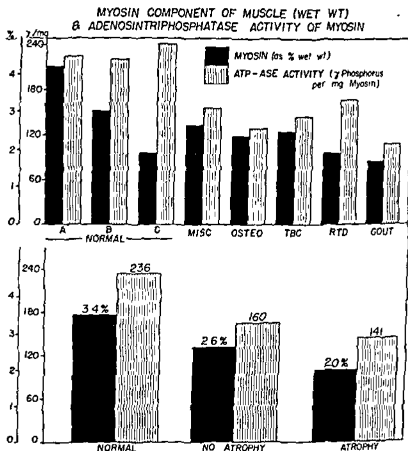


Fig 100 Comparison of the myosin content of wet muscle, and the adenosinetriphosphatase activity of this myosin, in normal subjects with that in patients with various diseases

according to the presence or absence of muscle atrophy regardless of the disease In each category the thirteen normal persons were included for reference The normal persons whose muscles were free of cellular foci are labeled A, those with doubtful lesions, B, and the normal subjects with definite muscle nodules, C To simplify the graphic presentation, only the more significant chemical constituents are included. In Figure 98 is shown the protein fraction of the dried muscle As compared to the normal subjects, in whom 74 per cent of the dry weight of muscle is made up of protein, there is a significant decrease in the cases of miscellaneous diseases, of gout, and especially of degenerative joint disease or osteoarthritis where

the level falls to 51 per cent. It should be pointed out, however, that in this last group, the average age was sixty-nine years. In the patient with gout, it was sixty-five and in the normal subjects it was forty-four years. With advancing age, the general nutritional state declines and skeletal

but are sick and in most instances bedridden, with rheumatic or nonrheumatic diseases.

It was of interest to know whether the diminution of the protein fraction was attributable to a loss in any particular one of its components. In Figure 99 the collagen and myosin components of muscle protein are demonstrated. It is noteworthy that as the myosin fraction* falls in the various groups, there is no compensatory increase in collagen concentration even in diseases associated with marked atrophy. From this it is concluded that atrophy in human skeletal muscle is not associated with a process of replacement fibrosis.

Although there is a significant fall in the myosin content of muscle from patients with various diseases, it cannot be concluded that this change is characteristic of any particular disease. It appears to be related to disease in general and to muscle atrophy in particular. An exception to

of these so-called "lesions." We are now further challenged by the observation that the myosin content of the muscle of these same persons is significantly lower than in those normal subjects whose muscle sections were free of cellular infiltrates or even in those who had "doubtful" nodules. The number of individuals in each subgroup is small and conclusions from this histochemical correlation are not warranted at this time, although the observation seems worthy of further investigation.

In Figure 100 is shown the myosin content of the wet weight of muscle and the adenosinetriphosphatase activity of this myosin. It is only an accident resulting from the scale used in this graph that the column of the enzyme is higher than that of the myosin. The myosin as per cent of wet weight decreases in the same order, as shown in Figure 99. The adenosinetriphosphatase activity, like the myosin, falls nonspecifically in the various diseases. The determining factor again seems to be essentially disuse and muscle atrophy. Unlike myosin, however, adenosinetriphosphatase activity does not vary with presence or absence of cellular foci in the muscle of normal persons. It is noteworthy that in the various groups the fall of myosin is not parallel to that of adenosinetriphosphatase. In fact, in some instances the values are divergent. This finding supports the contention of some investigators that myosin and its adenosinetriphosphatase activity are due to separate substances, the enzyme being adsorbed to the surface of the myosin.

* The term myosin as used in this report means that protein fraction extracted from muscle with 0.5 molar potassium chloride in 0.03 molar sodium bicarbonate precipitated by a ten fold dilution in copper-free water at a pH of 6.8.

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DISCUSSION

HUGO A. FREUND

Dr. Bunim and his associates question the specificity of muscle nodules in rheumatoid arthritis. In that, they are not alone. They agree that these nodules are found in higher percentage in rheumatoid arthritis, and that they are present chiefly in rheumatic diseases. Although one illustration shows similar nodules in muscle taken from a healthy person, I hardly *think he would have us believe that such accumulations of* lymphocytes and plasma cells are normal muscle constituents, or that a latent disease was not present.

Our original papers cited Klinge, and *Curtis* and *Pollard*. Klinge *concluded* "that in rheumatic fever (fieberhafter Rheumatismus), vascular connective tissue of the entire body is attacked in devastating fashion (in verheerender Weise), with or without involvement of the joints." Rheu- [illegible]

investigators. It was undertaken primarily to make a study of the central *and peripheral nervous system in rheumatoid arthritis.* I shared the belief of clinicians that rheumatoid arthritis was a systemic disease, and that the pathology of the joints, the subcutaneous nodule and the heart did not *represent the entire pathology.*

A search of the literature disclosed the fact that nervous tissues had not been adequately studied. I thought that the interosseous muscle atrophy, hyperactive reflexes, paresthesias and trophic changes might find explanation in a histologic study of the entire nervous system. That was the objective of our original work published in 1942 on peripheral nerves and in 1945 on muscles. Discrete nodules in the epineurium and perineurium of peripheral nerves were found in more or less zonal arrangement in five of seven autopsied cases of rheumatoid arthritis. It was pointed out that these nodules were present in nerves not connected with involved joints, such as the ilio-inguinal.

In continuing our search for nodules in the smaller nerve branches,

muscle tissue was examined. We found the epimysial and perimysial accumulations of lymphocytes in widely scattered areas. In the preliminary report in *Science*, only fourteen cases, all positive, were reported. We suggested that these nodules must be present in enormous numbers, that their presence was evidence that rheumatoid arthritis is a systemic disease, that further investigation was desirable. Later, in twenty-eight cases of rheumatoid arthritis, positive findings were made in all cases except one, in which a typical lymphocytic area was found, and in which a review of the history revealed a record of rheumatoid arthritis many years previously. In subsequent papers and exhibits we have shown lymphocytic accumulations adjacent to trichinosis and in muscle material from cases of disseminated lupus very closely resembling that derived from rheumatoid arthritis. We have not found these nodules in pure spondylitis uncomplicated by clinical rheumatoid features.

We believe that the pathology in disseminated lupus in the area surrounding the muscle nodules and often in the nodules themselves may be distinguished from that of the rheumatoid cases, but that it is very difficult in some instances. Most of all, we wish to emphasize that we have never found nodules in disseminated lupus in peripheral nerves. Our position has simply been that the histopathologic studies must be taken together as a contribution to the total pathology of rheumatoid arthritis. Furthermore, even accepting the criticism of specificity raised by Dr Bunim's paper and by a few others, it has been shown that biopsies in suspected rheumatoid cases may yield confirmative evidence before joint involvement is manifest, and may therefore be of value.

Further study may cause us to modify our original opinion. Certainly, the paper of Dr Bunim shows a preponderating presence of lymphocytic accumulation in cases of rheumatic disease. It may be that the etiologic agent—infection, hormone, enzyme, metabolite, allergy—may incite the pathologic entity under discussion, and that the subsequent course of the disease in a patient may be modified by other still unknown factors. The presence of a positive finding adds confirmative evidence, and further careful study, together with other tests, may assist in differentiating forms of rheumatic disease.

OBSERVATIONS ON THE HISTOPATHOLOGY OF THE NEUROMUSCULAR SYSTEM IN RHEUMATOID ARTHRITIS

L. RAYMOND MORRISON, PEDRO M. CATTOGIO AND WALTER BAUER

Histologic examination of the neuromuscular system was undertaken in patients with rheumatoid arthritis in an attempt to establish the anatomic basis for the various muscular, neurologic and neurologic-like symptoms and signs that frequently accompany this disease. Similar examinations were made in cases of lupus erythematosus disseminatus, dermatomyositis, periarteritis nodosa, scleroderma and rheumatic heart disease without pathologic evidence of arthritis, to determine the specificity of the lesions observed

CLINICAL MATERIAL

Tissue was obtained from eighty-two cases of rheumatoid arthritis In thirty cases only muscle biopsy specimens were examined Of the fifty-two autopsy cases, the muscles were examined in twenty, the peripheral nerves in forty-seven, the sympathetic chain in nineteen and the spinal cord in thirty-nine Somewhat comparable studies were made of tissues obtained from nine cases of lupus erythematosus, five cases of dermatomyositis, two cases of periarteritis nodosa, one case of scleroderma and four cases of rheumatic heart disease without pathologic evidence of arthritis.

FINDINGS

The principal lesion found in this study was the paravascular focal collections of lymphocytes and plasma cells in the connective tissue sheaths of muscles and nerves Similar lesions have been reported by previous workers from the latter part of the last century onward [1] Except for a few cases reported in the literature[2] these focal cellular collections have not been observed in the many control cases examined by various workers [3] In fact, so specific are these lesions thought to be that Steiner and colleagues are able to distinguish by the character of the foci alone the lesions of rheumatoid arthritis from those seen in other diseases.

As far as [illegible] concerned, it is true that focal accumulations [illegible] well as by us in Raynaud's [illegible]ty of other conditions, as [illegible]otor disturbances are common to many diseases and it is possible that the cellular infiltrations are related to these disturbances

Rheumatoid Arthritis We have found these paravascular round cell aggregations in about 60 to 75 per cent of the cases in which muscles were examined (depending upon whether the tissue was obtained by biopsy or at autopsy), and in about 70 per cent of the cases in which nerves were examined.

These paravascular foci were found in patients with rheumatoid arthritis who ranged from eight to seventy-six years of age, there was no relationship with the severity of disease, its state of activity, or its duration.

LESIONS IN MUSCLES As previously described,[9] the focal lesions in muscles in rheumatoid arthritis were always located in the interstitial connective tissue usually of the perimysium but sometimes of the endomysium (*Fig* 101 *a*). Ordinarily such a focus would be in relation to a blood vessel The

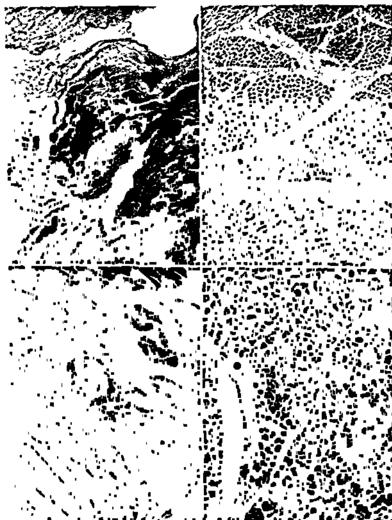


Fig 101 Similar foci of lymphocytes and plasma cells in endomysium or perimysium of muscle *a*, rheumatoid arthritis, *b*, lupus erythematosus disseminatus, *c*, dermatomyositis, *d*, scleroderma (Hematoxylin and eosin, ×100)

cells in the infiltration were in most instances lymphocytes, with a smaller number of plasma cells or monocytes participating These collections were present not only in muscles that were related to joints but also in an extraocular muscle and in the diaphragm

Atrophy of the muscle fibers varied from case to case and bore no rela-

tionship to the presence or absence of these cellular foci. Sometimes atrophy was not present at all, in other cases it was moderate, with variation in size of the fibers, relative increase in sarcolemmal nuclei and loss of cross striations. In severe atrophy long chains of sarcolemmal nuclei were present, lying deep in a muscle fiber, if muscle fiber still remained, otherwise forming dense cords in thin strands of fibrous tissue in the site of what were presumably former muscle fibers.

LESIONS IN NERVES Similarly, in the nerves the lesion was located in the connective tissue sheaths, the endoneurium, the perineurium or epineurium The nodules themselves were similar to those seen in muscle. Since the nerve sheaths are the peripheral extensions of the meninges of the central nervous system—the endoneurium being derived from the pia, the perineurium from the arachnoid and the epineurium from the dura—the meninges themselves were examined for focal accumulations of round cells In the subarachnoid space, seen best in relation to nerve roots, there were increased r
arthritis. T
present in
advancing age However, comparing the rheumatoid arthritis cords with the normal control series of similar age groups, the number of cells in the meninges is greater in the rheumatoid arthritis cases We have not yet encountered frank foci such as are found in nerve sheaths, but this is being further investigated.

In addition to lesions in the interstitial tissue of nerves there are sometimes mild parenchymatous alterations to be found as well In a myelin stain patches of pallor and beading and fragmentation of myelin can be seen Sometimes this is verified by a positive Sudan reaction It must be emphasized that these changes are not severe, that they are scattered, and that they bear no obvious relationship to focal inflammatory reactions in the nerve sheaths Here again, as in the cord and axon alterations to be described, these changes were not specific, and were similar to, but more severe than, corresponding changes as they develop in advancing age In a scattered way also swelling, tumefaction and fragmentation of axons were observed in silver preparations Axon alterations were also found in the posterior roots in some cases

Due to injury to the axons, retrograde cell disease was present in the large motor cells of the anterior horns of the spinal cord in about 25 per cent of the cases Instead of the cells being concave in outline with centrally placed nucleus and even distribution of Nissl substance, these affected cells were swollen, with convex outline, central chromatolysis, eccentric nucleus and sometimes increased lipochrome Sometimes similar changes are noted in old age but they are more advanced in rheumatoid arthritis, for example, in one case in which the changes were quite severe, the patient died at the age of eight years having had rheumatoid arthritis for over six years

In the sympathetic chain of the autonomic system cellular reactions were also found These reactions took place within the ganglion itself, or along the chain between the ganglia, or as lymphoid infiltrations in the neighboring fat. Within the ganglion itself, it is probably true that some of these cellular collections, specifically those surrounding or replacing nerve cells, were composed of modified glial elements as has been recently stated,[7] but

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the focal collections of round cells were found in the muscles in eight out of nine cases of lupus erythematosus as well as in the peripheral nerves and sympathetic chain of the cases examined. These focal aggregations of cells (Fig. 101 *b*) were indistinguishable from those seen in rheumatoid arthritis, composed as they were of lymphocytes and plasma cells located in the interstitial tissue of the muscles or nerves

Dermatomyositis In dermatomyositis there were also interstitial accumulations of round cells in the connective tissue of nerves and muscles (Fig 101 *c*) They were found in all five cases in which muscle was examined. In one case the inflammatory reaction was extensive and one focus might be so large that it would extend beyond the limits of a low power field of the microscope In this way it seemed to differ from other diseases of this group But in other cases, the focal lesions were small and could not be distinguished from those of rheumatoid arthritis or lupus

Scleroderma The focal lesions found in the muscle of one case of scleroderma (Fig 101 *d*) presented no characteristics that distinguished them from those of other diseases of this group

Rheumatic Heart Disease The focal accumulations of cells found in the interstitial sheaths of peripheral nerves in four cases of rheumatic heart disease were similar to those found in rheumatoid arthritis. They were composed of lymphocytes and plasma cells with an occasional monocyte, usually seen paravascularly Occasionally the outer coat of the blood vessel would be slightly infiltrated.

Periarteritis Nodosa The inflammatory lesion of muscle in periarteritis nodosa is probably different from the lesion in these other diseases, because of the invasion of the blood vessel wall by polymorphonuclear leukocytes and destruction of the vessel wall In the foci in rheumatoid arthritis the vessels also sometimes showed infiltration of the outer coats by lymphocytes

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JOINTS AND PERIARTICULAR TISSUES IN IMMOBILIZED EXTREMITIES*

EUGENE F TRAUT, KENNETH M. CAMPIONE AND JOHN P. KISELIS

Extremities immobilized by paralyzing diseases or fixation apparatus frequently develop deformities. The joints in the involved leg or arm assume a bizarre position Forcible movement of the deformed extremity is often painful The associated muscular atrophy and contractures accentuate the distortion One of the deformities following a cerebrovascular accident is referred to as "posthemiplegic arthritis" without more evidence than joint *deformity, stiffness and pain on forced motion* [1-3] *Some refer to the joint* changes as "joint affections" in hemiplegia or call them "arthropathies."[4, 5] Some classify the condition as neuropathic arthritis, along with Charcot's joints in tabes [6] The joints on the paralyzed side are described as sometimes becoming red, swollen and hemorrhagic within a month of the "stroke"[7] "Arthritic changes" contribute to the stiffness of the paralyzed extremity [1] In discussions of changes in immobilized joints, it has been stated that use is indispensable to normal growth of cartilage [8] The noncontiguous joint surfaces have shown degeneration [9] The integrity of articular cartilage is dependent upon apposition with the opposing cartilaginous surface.

The painful, rigid extremities in Parkinson's disease have often been mistaken for arthritis An interosseous atrophy similar to that in rheumatoid arthritis occurs not infrequently in Parkinson's disease but has received little attention The pyramidal rigidity in the hemiplegic extremity, the extrapyramidal stiffness in Parkinson's disease, and the leg or arm coming out of a cast resist passive motion just as do the stiff extremities of the arthritic

Our interest led us to study just what makes the extremity resist outside efforts to move it, and, in particular, how much joint changes contribute to stiffness In dealing with these stiff extremities we considered the possible role of the recently investigated soft-tissue changes in stiffening diseases, notably the perineural and perivascular infiltrations in rheumatoid arthritis,[10] the abnormal effects of the autonomic nervous system expressed in the shoulder-hand syndrome or Sudeck's atrophy,[11] and the debated problem of fibrositis Venous and lymphatic stasis in immobilized extremities lead to intra-articular serofibrinous exudates Their organization causes adhesions of the capsular folds, according to an orthopedic viewpoint.[12]

CLINICAL MATERIAL AND METHODS

Our material included ten hemiparetic or hemiplegic patients, six patients with Parkinson's disease, a patient with congenital palsy, and a bedridden patient with tabes, who had Charcot's joints in both knees All of the hemiplegic patients had long-standing arterial hypertension and arteriosclerosis One was a young man with rheumatic valvulitis who developed hemiplegia as a result of cerebral embolus. We included the patients with tabes to determine possible changes in the soft tissues at some distance from his joints

* Assistance and advice were kindly given by G M. Hass, M D, and Granville A Bennett, M D

The joints of the deformed extremities were examined for swelling, tenderness and mobility. Roentgenograms were studied for evidence of intra-articular changes such as narrowing of the joint spaces, alteration of the normally smooth bone ends or blurring of the joint margins. In most of the patients with hemiplegia, biopsies were made from gastrocnemius muscles on the paralyzed and nonparalyzed sides One biopsy was taken from the gastrocnemius in the patients with Parkinsonism, one from the patient with congenital cerebral palsy and one from the patient with Charcot's knee joints

GROSS MORPHOLOGY

The deformities found were those of flexion (often to the point of subluxation), stiffness and atrophy of the hand muscles Most deformities in the upper extremity in both hemiplegia and Parkinsonism included flexion at the metacarpophalangeal joints and extension of at least some of the interphalangeal joints, although there was wide variation in the finger deformities In all except two patients the flexion and extension deformities could be easily reduced with only slight discomfort to the patient

The flexion deformities in the hands of two patients with Parkinson's disease could not be reduced The deformities in these patients were especially marked but roentgenography did not disclose any arthropathy other than the subluxation noted in the other cases The bones in the paralyzed hands in a few of the hemiplegic patients were smaller than those on the nonparalyzed side The bones in the paralyzed hand were especially small in the patient with the birth palsy Roentgenologically the deformities were again apparent and were more easily distinguished as partial dislocations.

Osteoporosis was a regular finding and could be distinguished in the roentgenograms of all our elderly patients It was the generalized rarefaction usually characterized as senile osteoporosis In some of the hemiplegic cases it seemed more marked on the paralyzed side In the arm of one hemiplegic woman (V H) it appeared as a patchy loss of density of the Sudeck type None of these patients had been given thiocyanate while under our observation

HISTOLOGY

Histologically the atrophy of the soft tissue was expressed as narrowness of the muscle fibers The atrophy of the muscle fibers was most evident in the preparations from the hemiplegic patients and was much less apparent in the biopsies from the patients with Parkinsonism The biopsies also showed an increase in the nuclei between the muscle fibers of all the stiffened extremities This increase in the interfibrillar nuclei seems to be an increase in the number of sarcolemmal nuclei The nuclei vary in shape and tend to be oval or rounded The increased number of nuclei is not explained by the atrophy of the muscle and the consequent compression of [illegible]

in bone destruction A similar increase in the number of sarcolemmal nuclei has been described in muscles degenerating as a result of denervation The apparent increase in sarcolemmal nuclei has been explained as

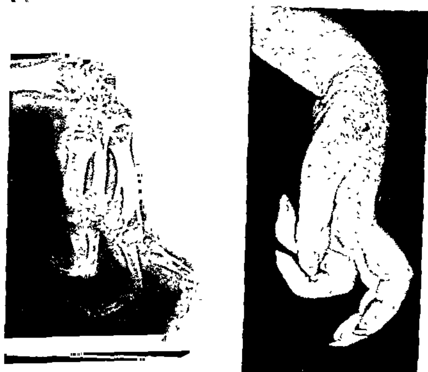


Fig 102 Hand of patient V H (Case II), hemiplegic side The roentgenogram shows subluxation and Sudeck's atrophy but no arthritis

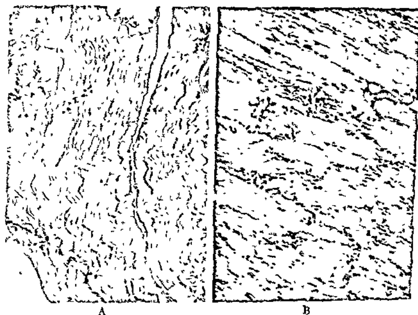


Fig 103 Sections from gastrocnemius muscles of patient V H. A, muscle from nonparalyzed side, B, muscle from paralyzed side, showing increase of interfibrillar nuclei

due to the decrease in bulk of fibrils The infiltration of mononuclear cells ... muscle Brown ... were present

CASE STUDIES

increased.

Case II A woman of sixty-four years (V H) with arterial hypertension had hemiplegia due to cerebral hemorrhage two years previously She had never had

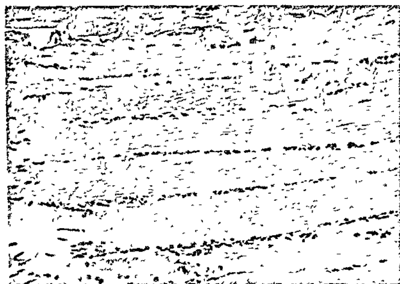


Fig 104 Section from gastrocnemius muscle of patient A S (Case III), showing little change in muscle fibrils but some increase in perimysial nuclei The patient had idiopathic Parkinsonism

arthritis Roentgenography showed some subluxation of her finger joints (Fig 102) The joint ends were smooth, the interspaces were normal width A microscopic section from her paralyzed leg (Fig 103) shows a great concentration of sarcolemmal nuclei and interfibrillar wandering cells

... seven years (A S.) had idiopathic Parkin- ... minimal ... terminal ... Fig. 104)

Case IV R F was a physician seventy-five years old. He had had Parkinson's disease, probably owing to arteriosclerosis, for eight years His metacarpophal-

angeal joints were flexed The distal phalanges were flexed and deviated to the ulnar side Roentgenograms show *flexion deformities* to the point of subluxation in the knuckles (Fig 105). No arthritis was *detectable* on physical examination Histologically there are marked general and focal interfibrillary accumulations of



Fig 105 Hands of patient R F (Case IV), with Parkinsonism The hand deformities and interosseous atrophy are apparent, and the roentgenogram shows subluxation but no arthritis

sarcolemmal nuclei (Fig 106) In places the nuclei are so grouped as to resemble giant cells Fat cells frequently interrupt the continuity of the muscle fibers.

Case V. A man of fifty years had been paralyzed since birth by a congenital

left hand were less than one-quarter the size of the bones on the right B showed the muscles of the left side markedly infiltrated with wandering cells

Fig 106 Section from gastrocnemius muscle of patient R F, showing general and focal accumulations of interfibrillar nuclei, and muscle fibers interrupted by fat cells

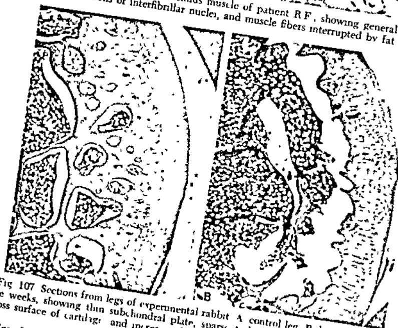


Fig 107 Sections from legs of experimental rabbit A, control leg, B, knee immobilized nine weeks, showing thin subchondral plate, sparse trabeculae, connective tissue layer across surface of cartilage and increase of cartilage cells

Case VI A patient with tabes, who had marked Charcot's joints affecting the knees, had been bedridden three years The fibers of the muscles in his leg were

normal in width Cross striations were obliterated The interfibrillary nuclei were increased, many of them being very large, pale cells. The small arteries were infiltrated by round cells, the appearance being compatible with syphilitic arteritis

IMMOBILIZATION EXPERIMENTS WITH RABBITS

One of the anterior extremities of each of six rabbits was immobilized. At first we strapped the foreleg to the chest. This gave satisfactory immobilization but many of the rabbits died of pneumonia We adopted the better method of applying a plaster cast fixing the rabbit's foreleg in extension The rabbits were then sacrificed at periods varying from five to twelve

Table 48. Summary of Results of Experiments with Rabbits

RABBIT NO	WEEKS IMMOBILIZED	GROSS CHANGES IN LEG	CHANGES IN CARTILAGE	CHANGES IN BONE	CHANGES IN MUSCLE
1	5 Flexion	No change	Normal	Atrophy	Atrophy, slightly increased nuclei; fragmentation
2	8 Extension	Disarticulated at joint with cartilage exposed	Vascularization	Atrophy	Atrophy
3	9 *Extension*	Muscular *atrophy; stiffness, crepitus*	Connective tissue *overgrowth*, subsynovial inflammation	Atrophy, narrow, *sparse* trabeculae; subchondral plate thin	Fibrils narrow, nuclei increased, vary in shape
4	10 Extension	Atrophy, stiffness	Defects in surface, slight *connective tissue* overgrowth	Atrophy	Atrophy
5	12 Extension	Atrophy, stiffness, crepitus	Connective tissue overgrowth	Atrophy	Atrophy; increased nuclei
6	12 Extension	Atrophy, stiffness, crepitus	Connective tissue overgrowth	Atrophy	Atrophy, increased nuclei

weeks The immobilized and the opposite knees, with their attached muscles, [illegible] and compared. Findings are summarized in Table 48.

[illegible] was

[illegible] ophy

[illegible] pear-

been immobilized in a plaster cast for [illegible]

ing is the atrophy of the bone, the subchondral plate being almost entirely

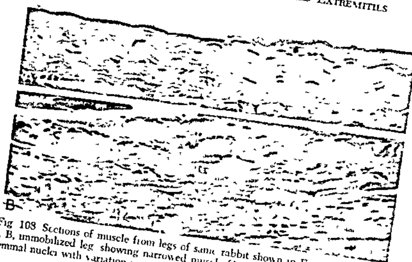


Fig 108 Sections of muscle from legs of same rabbit shown in Figure 107 A, control leg, B, immobilized leg showing narrowed muscle fibrils and increase in number of sarcolemmal nuclei with variation in size shape and intensity of stain

A

B

Fig 109 Sections from legs of experimental rabbit A, control leg, B, leg immobilized twelve weeks (higher magnification) showing almost no subchondral plate, sparse trabeculae, marked proliferation of articular cartilage with atypical arrangement of cells, and centripetal growth of connective tissue across cartilage with villuslike protrusion

absent The trabeculae are narrow, short and sparse. A proliferation of connective tissue proceeds from the periphery toward the center across the surface of the cartilage The cells of the articular cartilage are increased.

Sections of muscle from the same rabbit (Fig 108) show that the muscles are more granular on the immobilized leg, the average width of the fibrils being 20 microns as compared with an average fibril width of 36 microns in the control leg The sarcolemmal nuclei, besides being increased in number, vary markedly in size, shape and intensity of stain

Figure 109 shows sections from the legs of a rabbit which had carried a cast twelve weeks. The findings as regards atrophy of subchondral bone, the centripetal growth of connective tissue over the cartilage and the muscle atrophy are similar to but more marked than those in the leg immobilized nine weeks. At one point the connective tissue protrudes into the synovial cavity in the shape of a villus In addition, new cartilage has been seen *proliferating between the articular cartilage and the overlying connective tissue layer.*

CONCLUSIONS

The term "posthemiplegic arthritis" is not justified by our findings. Arthritis is not a part of the deformity in Parkinson's disease.

Marked soft-tissue changes are demonstrable histologically in hemiplegic extremities and in congenital palsy Similar changes are less marked in the muscles of Parkinson's disease

Proliferation of the cartilage and synovium is demonstrable in the joints of rabbits' legs immobilized in casts

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ABSTRACT

THE RANGE OF PATHOLOGIC REACTIONS WHICH CAN BE DISPLAYED BY HUMAN SYNOVIAL TISSUES--A CONTRIBUTION TO THE STUDY OF SPECIFIC LESIONS

DOUGLAS H COLLINS

Observations based on histologic study of 250 synovial membranes have been collated under three headings changes in synovial cells, vascular and exudative phenomena, and leukocytic reaction

Synovial tissues are mesenchymal and display many of the same fundamental reactions as simple connective tissues elsewhere, e g , atrophy, hyperplasia, degenerations and mutations Particular properties of synovial cells are the production of extracellular mucin, histiocyte differentiation and the ability to form endothelium-like surfaces These properties can occasionally be shown by extra-articular connective tissues, but the study of synovial neoplasms suggests that they may be inherent qualities of joint tissues

The rich capillary vasculature of synovial membrane is only revealed in hyperemia The loose-textured tissue and the synovial sac are easily and quickly distended by transudate or exudate Vascular and exudative phenomena seemingly develop out of proportion to the severity of the inflammatory stimulus and are rarely localized to one part of the membrane

Normal synovial tissues contain very few leukocytes Light perivascular lymphocytic diffusion is an early reaction to traumatic and other forms of synovitis Discrete perivascular foci are the maximal reaction seen in chronic trauma and osteoarthritis. Great numbers of lymphocytes are seen only in severe and chronic inflammations, e g , tuberculous and rheumatoid arthritis, or together with neutrophils in subacute suppurative synovitis Very large lymphoid foci and follicles seem to occur only in chronic progressive (rheumatoid) arthritis, where there is also synovial proliferation Plasma cells may replace lymphocytes Eosinophil infiltration is rare Neutrophils predominate in pyogenic infections but are also present in rheumatoid and rheumatic fever arthritis

Rheumatic fever synovitis is characterized by hyperemia, edema, fibrinous exudate, focal fibrinoid necrosis, neutrophil reaction and little proliferation The rheumatoid lesion has affinities with subacute or chronic bacterial arthritis but also shows features of its own Histologic diagnosis of rheumatoid arthritis is justified, but etiologic deductions are still speculative and can be made by analogy While comparisons are valid between different synovial lesions in man, caution is needed in comparing reactions in synovial and extra-articular tissues and in applying to man the results of experiments on small animals

DISCUSSION*

Those of us who deal primarily with morphology are frequently pressed by our colleagues in clinical medicine to provide interpretations that can be used to differentiate one disease from another In some disorders the patterns of reaction are disease-specific but in other situations the morphologic changes may cover a wide range of exudative, degenerative, and proliferative phenomena that are exceedingly difficult to interpret Unfortunately it is in the group of conditions in which the etiology is obscure that the pathologist most often is unable to point out criteria upon which a definitive diagnosis can be made

Dr Collins has stated that very large foci, or even follicles of lymphocytes, "seem to occur only in rheumatoid arthritis or at least in joints where the chronic pro-

* By Granville A Bennett

an average. The effects on these patients of their stay in this microclimate for so long a time—they were not allowed to leave the room during the whole of their stay there, and the staff and visitors entered the room by the air lock—were then investigated

RESULTS

The skin temperature of the patients was determined on different parts of the body with a thermocouple of copper and constantan [4] The measurements were made before and after the stay in an ordinary room temperature of 20° C and relative humidity of 50 per cent, and in the hot room We found that at ordinary room temperature these patients—especially those with rheumatoid arthritis—showed a relatively low skin temperature on the distal parts of the extremities and a higher difference between this skin temperature and that of the trunk than normal persons. In the hot room this skin temperature rose much more on hands, feet and distal parts of the extremities—just as far as the effect of the arteriovenous anastomosis extended—than on the trunk, so that the difference was inverted, skin temperature being higher on the distal parts than on the central The peripheral vasospasm was converted into peripheral vasodilatation The peripheral circulation was increased, and the arteriovenous anastomoses were maximally dilated [4] In addition, in the hot room the consensual reaction of the vessels to ice on the skin, inhalation of amyl nitrite, etc, was lowered or in some cases inhibited

The relative oxygen saturation of venous blood was also affected [5] At ordinary room temperature mean oxygen saturation of venous blood, measured at the median cubital vein, was 51 per cent on an average That is a low saturation In normal individuals Lundsgaard[6] found an oxygen saturation of 68 per cent under the same conditions, and several other authors[7] have found values around 65 to 70 per cent This relatively low saturation in venous blood can no doubt also be considered in association with the constricted peripheral circulation in these arthritic patients.

At a room temperature of 32° C we found, on an average, 82 per cent mean oxygen saturation Goldschmidt and Light had observed that by keeping the forearm in hot water at a temperature of about 45° C, a relative oxygen saturation could be established in venous blood, measured in the same way, of up to 92 per cent, that is, bordering on that of arterial blood. By keeping the forearm in water at a temperature between 29° and 39° C. we were unable to obtain an oxygen saturation in these veins of more than 69 per cent, or, by keeping it in air up to 32° C, of more than 75 per cent The difference lies in the length of stay in the room and also in the constancy of the temperature, this seems to be the reason that we obtained a stronger effect

The abnormally low saturation of the venous blood in these arthritic patients seems to be associated with the peripheral vasospasm When this vasospasm vanished in the hot room and was converted into vasodilatation, the saturation was good It seems that the maximal dilatation of the arteriovenous anastomoses and of the capillaries in the hot room was responsible for the high saturation found, approximating the saturation of the arterial blood.

The venous blood taken from the cubital vein in the hot room was bright

red, a similar phenomenon has been observed by many physicians i tropics This color was caused by the high oxygen saturation of the ve blood, and could also be achieved at a room temperature of 20° C. if saturated the venous blood with oxygen It was then possible to conf the hundred-year-old assumption of Mayer, which we had thought incorre

The hemoglobin percentage was unchanged in the hot room

With a Millikan apparatus we have also begun to measure the tensio of oxygen in the tissues of our arthritic patients outside the hot room, bu it is too early to report the results The values, however, seem to be in the same direction as those in the venous blood.

The cardiac output per minute was also investigated before, during and after the stay in the hot room Patients with normal heart function showed no statistically significant changes when in the room In some patients with cardiac insufficiency we observed good compensating effect from the stay in the hot room Here the diminished active peripheral resistance to blood flow at this higher temperature seems to be of importance *

Broadly speaking, no changes in calorie consumption and basal metabolic rate have been observed However, there have been some individual variations [1] In some cases a slight increase in the calorie consumption was noticed during the weeks immediately following admission to the hot room This observation agrees with that of Knipping[9] in the tropics

If a depression of the basal metabolic rate had occurred, i e, if the second chemical regulation of temperature had entered into function, it could have been expected to take place chiefly during the latter part of the stay in the hot room, when a certain amount of acclimatization ought to have been reached In some cases a slight depression of the total calorie consumption was observed during this latter part, but not in most cases Compare these results with those of Sundstroem[10] and others in the tropics

Cultures were made regularly from throat flora of all patients In thirty of them (twelve of the rheumatic fever cases and eighteen of the rheumatoid cases) these cultures on admission of the patients in the hot room had shown beta hemolytic streptococci In twenty-six of these, the cocci disappeared during the stay in the hot room In one additional case the cocci did not disappear during the first stay, but 5 years later the patient had a relapse, was given a second treatment in the hot room and then the cocci disappeared In three cases there was no effect Coburn has obtained corresponding results by removing persons from a temperate climate (New York) to a tropical climate (Puerto Rico)

All cases treated in the hot room were severe ones which had not improved earlier under ordinary internal and physical therapy The most obvious effects on the clinical symptoms were the diminished movement pains and tenderness After some days in the hot room the patients could walk and move about much better and more easily There was also a remission of the periarticular edema and the capsular swelling of the joints attacked The livid coloration of the skin on hands and feet vanished The patients had a better appetite and their weight increased In most cases the sedimentation rate diminished considerably Patients became afebrile if they had been subfebrile before Improved function was obtained in cases of cardiac insufficiency

Of the eighteen rheumatic fever cases, fifteen improved, became free from .

symptoms, and are at times capable of working Eleven of them, however, have deformities of their mitral or aortic valves. Two died of heart failure, one of nephritis and uremia

Of the twenty-nine rheumatoid arthritis cases, fifteen became free from clinical symptoms and are at times capable of working (one of them improved after the first treatment in the hot room, then had a relapse and was given new treatment, since then she has been free from clinical symptoms) Nine improved and eight of these are working at times; in one case there was a recurrence one year after the treatment Two cases improved temporarily but deteriorated again. One case improved during the first treatment but had a relapse after return home four months later and could not be improved by renewed treatment in the ward. In two cases there was no effect

In no case was there a tendency to recurrence immediately after return to ordinary room temperature. In some cases, however, hemolytic streptococci were again found in the throat flora after a few days

The clinical findings, however, seem to me not so important as the physiologic and bacteriologic effects Three such effects have special importance *as results of the stay of the patients in the hot, dry microclimate.* (1) changes in peripheral circulation, (2) changes in the oxygen saturation of venous blood, and (3) changes in the throat flora.

caused by the physio- e shall find an expla- throat flora, and diseases caused by such streptococci, are relatively uncommon in a tropical climate I say "tropical climate" and not "the tropics," since it is the climate and not the latitude that seems to be of importance.

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THE PERIPHERAL GENESIS OF PAIN

JONAS HENRIK KELLGREN

We have little precise information about the mechanisms by which disease processes cause pain The immediate pain of a cut or burn clearly results from direct mechanical or thermal stimulation of the pain nerves, but when discussing the pain of disease we usually speak about "inflam-

mation," "tissue tension" or muscular or vascular "spasm" though we have no clear conception of how the pain is produced

Most clinicians have been impressed by the fact that severe structural and functional disorders of the body are often quite painless, while in many painful states such disorders may be insignificant This mysterious lack of correlation between pain and pathology has led to the invention of special neurologic mechanisms for the genesis of pain Such concepts have gained impetus from the study of causalgia, and the occasional relief of pain that follows sympathectomy, but true causalgia is far from common and it is probably unwise to base a general concept of pain upon such a bizarre rarity

In the common painful diseases that we see every day, experience tells us that efficient treatment of the diseased organ commonly relieves the pain This suggests that local tissue factors are a more potent cause of pain than "vicious circles" and other mechanisms within the nervous system We are therefore studying these local factors, whether chemical, circulatory or morphologic, which may contribute to the pain of disease

From the outset it was clear that we were dealing with two major mechanisms first, the direct stimulation of normal pain receptors by excessively strong stimuli, and second, a lowering of threshold so that pain results from stimuli normally ineffective An examination of the pain produced by various chemical changes will serve to illustrate this point

CHEMICAL CHANGES

Various pain producing solutions were injected into the forearm muscles of four normal subjects and the result was noted in terms of spontaneous pain and alteration of pain threshold to mechanical stimuli as measured by a pressure algesiometer

The solutions contained elements normally present in the body, e g, sodium chloride, glucose, hydrochloric and lactic acid, sodium carbonate and sodium hydroxide, potassium chloride, and calcium chloride They were made up in such a way that only a single factor was studied in each experiment alterations of osmotic pressure, alterations of *p*H, and so on A standard dose of 0 3 ml was injected and the immediate and delayed results were noted. Figure 110 summarizes these results It will be noticed that with hypertonic solutions there is a short latent period followed by severe spontaneous pain but no alteration of pain threshold to mechanical stimuli With acids there is immediate pain accompanied by a lowering of threshold to mechanical stimuli, and this low threshold may persist for as long as twenty-four hours Alkalis produce similar change but are less effective than acids Excess potassium chloride gives a similar result, but excess calcium chloride produces a delayed lowering of threshold although no immediate pain is experienced

Thus certain physiochemical disturbances in the tissues may give rise to spontaneous pain alone while others may produce an alteration of pain threshold. The majority of such changes, however, produce a combination of spontaneous pain with an alteration of threshold

THERMAL CHANGES

An alteration of pain threshold to mechanical stimuli is easily recognized because it gives rise to pain on movement and pain on pressure.

Alterations of pain threshold to thermal stimuli are less easily recognized, and the fact that cutaneous pain and deep pain behave differently in this respect introduces a further complication.

In nerve blocking experiments we found[1] that sensibility to deep pain and sensibility to cutaneous pain may be dissociated, and that deep pain sensibility is peculiarly susceptible to cooling. Further studies showed that when the ulnar nerve is cooled at the elbow, spontaneous deep pain is felt in the hand during the onset of deep analgesia within the ulnar territory,

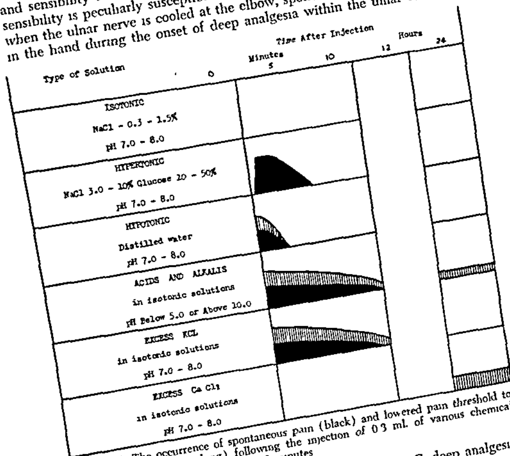


Fig 110 The occurrence of spontaneous pain (black) and lowered pain threshold to mechanical stimuli (hatching) following the injection of 0.3 ml. of various chemical solutions into the forearm muscles at 0 minutes

but when the temperature of the nerve approaches 10° C. deep analgesia becomes complete and the pain ceases. Local cooling of the deep tissues is also accompanied by pain while the tissue temperature is falling through the range of 30° to 15° C., but as cooling proceeds the tissues become analgesic and the pain fades away in spite of further cooling.

In the normal subject only rapid and profound cooling causes pain, while slow cooling merely produces analgesia without preceding pain. If, however, the deep pain nerves are abnormally sensitive, even slow cooling through the temperature range of 30° to 15° C may cause severe pain.

In the normal subject cutaneous pain results from extremes of temperature above 45° C and below 10° C., while deep pain only results from rapid cooling within the range of 30° to 10° C.

In the erythralgic condition described by Lewis,[2] both warming and cooling produces cutaneous pain within a much wider range of temperature, above 30° C. and below 15° C, but deep pain remains unaffected When, on the other hand, the deep pain nerves are abnormally sensitive, even gradual cooling within the range of 30° to 15° C causes severe deep pain, while the effects of extremes of temperature on cutaneous pain remain unchanged Thus, in cutaneous erythralgia extremes of temperature cause pain, while in deep hyperalgesia pain results from the cooling which occurs with ordinary everyday changes of environment These temperature effects are most easily demonstrated when the circulation to the part is occluded, so that they are clearly the result of the temperature change as such and are not caused by secondary circulatory disturbances

CIRCULATORY CHANGES

To investigate the effect of circulatory changes upon painful states we keep the temperature of the part constant and within the range of 30° to 35° C, and we then produce venous congestion or arterial occlusion by applying a pneumatic cuff proximal to the lesion, using pressures of 80 and 200 millimeters of mercury respectively Each pressure is maintained for ten minutes and any alteration in pain is noted

This simple test separates painful states into three groups In the first group there is no response, in that arterial occlusion and venous congestion have no effect whatsoever on either pain or hyperalgesia In the second group there is a dramatic build-up of pain during arterial occlusion, the patient becomes pale, sweating, and so acutely distressed that the cuff must often be released before the usual ten minutes have elapsed After

present In the third group there is a lesser or modified build-up of pain during arterial occlusion and also a variable increase of pain during venous congestion, and again a rapid recovery after release These tests are only useful when the patient is actually experiencing pain or has experienced pain recently When pain is very slight or if the patient is unstable or uncooperative, it may also be difficult to interpret the result, but a dramatic build-up is always unmistakable

CLINICAL MATERIAL

These simple thermal and circulatory tests have been tried out on patients suffering from a variety of painful states I am greatly indebted to my surgical colleague, Dr R P Jepson, and my assistant, Dr H St C C Addis, for most of the following clinical observations

There are three main types of cases First, there are those known to have morphologic changes in the pain nerves, conditions such as glomus tumors and digital neuromata All cases in this group show extreme lowering of pain threshold to mechanical stimuli, neither arterial occlusion nor venous congestion has any effect whatsoever, but if the deep pain fibers are involved there is severe pain on cooling within the range 30° to 15° C, and if cutaneous hyperalgesia only is present there is no abnormal response to thermal stimuli Thus these cases differ from the erythralgic condition de-

artery, the flow *returning to normal after several days of denervation*. More extended periods of denervation resulted in subcontrol blood flow values which appeared to parallel the extent of muscle atrophy. Denervated muscles exhibited a subnormal temperature and responded to diathermy with temperature increases greater than those observed with comparable doses on normal muscle. The twitch response of denervated muscle to *induction* shocks was slower than that of control muscle. This was due only in part to its subnormal temperature. The subnormal temperature, increased susceptibility to diathermy and the sluggish response of muscle at various times after denervation did not appear to be related to changes in blood flow. Both short wave and micro wave diathermy caused an increase in blood flow provided the dosage and mode of application were sufficient to cause an appreciable elevation of muscle temperature. The critical level of muscle temperature was approximately 43° C At muscle temperatures significantly below this level diathermy appeared to exert little effect on blood flow

The application of heat by means of hot packs caused an increase in blood flow The effect of this type of thermogenic agent upon blood flow in denervated muscle or after local anesthesia with Butesin was less pronounced or nil

The effects of numerous drugs upon blood flow have been investigated. *Mecholyl, nicotinic acid, histamine, nitroglycerin, aminophylline, Isuprel* and small doses of epinephrine cause an increase in blood flow. Epinephrine in larger doses caused a decrease and dinitrophenol caused no change in blood flow In general, the effect of the various drugs upon blood flow was transient The increases in blood flow resulting from treatments with diathermy and hot packs were of much longer duration than those resulting from drugs, and the increases persisted after the return of deep tissue temperature to control values

* * *

ABSTRACTS

THE PHYSIOLOGY OF MUSCLE IN RELATION TO ARTHRITIS

DONALD YOUNG SOLANDT

The normal function of mammalian skeletal muscle depends on a normal skeleton. The muscular and skeletal systems have been matched during the develop-
(linear and volumetric), move-
ngth The arthritides alter these
with a profound effect on the
muscles involved

THE EFFECT OF SOME VASODILATNG AND VASO-CONSTRICTING DRUGS ON THE TEMPERATURE OF JOINTS AND RELATED STRUCTURES

JOSEPH LEE HOLLANDER AND STEVEN M. HORVATH

Measurements of intra-articular temperature have been made on nearly 100 persons, both normal controls and patients with various types of joint disease, using a filamentous thermocouple inserted through an aspirating needle into the knee joint Simultaneous measurements have been made of the joint temperature

The vasomotor responses in the synovial tissues are not necessarily parallel to those of the overlying skin but show a tendency toward a reciprocal blood flow between the integument and deeper tissues Procaine injected into the joint has shown a marked vasodilating action in some persons, but no effect in others. Other drugs administered included Priscoline, tetraethylammonium chloride, nitroglycerin, epinephrine, Neo-Synephrine, Pituitrin, Prostigmine and niacin Minimal effective dosages of these drugs did not significantly modify the joint temperature, presumably because the joints were already in a state of complete vasodilatation It appears that vasodilator drugs are incapable of raising the temperature in diseased joints beyond the limits delineated by the body temperature

INVESTIGATIVE STUDIES OF IMMUNE REACTIONS, ANTIGENS AND ENZYMES

STUDIES ON THE DIFFERENTIAL DIAGNOSIS OF ADULT RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS BY MEANS OF SEROLOGIC TESTS*

ROBERT W. QUINN AND SUNG J LIAO†

The differential diagnosis between acute rheumatic fever and acute rheumatoid arthritis in adult patients, based on physical findings alone, is frequently difficult because of the similarities of these two diseases The problem is further complicated by recent reports that an appreciable percentage of patients with rheumatoid arthritis have valvular heart disease Likewise other forms of arthritis, particularly osteoarthritis, are difficult to distinguish from rheumatoid arthritis, although it is granted that there may be mixed types Serologic tests have been employed by investigators and clinicians as aides in the diagnosis in these diseases The agglutination test with live beta hemolytic streptococci has been used for a dozen years as a diagnostic aid in the arthritides, singly or in combination with the antistreptolysin O test Cecil and his associates[1] and Dawson and his associates[2, 3] have used the agglutination test with live streptococci extensively, but with this test spontaneous agglutination, an inherent difficulty of the agglutination test employing live streptococci, has limited its use Both the antistreptolysin O and the antistreptokinase tests have been used widely in the study of beta hemolytic streptococcal infections and rheumatic fever However, there is still a need for laboratory procedures which might help to differentiate between arthritides and rheumatic fever in the adult

Recently two relatively new techniques for the determination of streptococcal antibodies have been introduced which seem to offer promise as aids in this difficult differential diagnosis The first, an agglutination test described by Thulin[4] employing autoclaved hemolytic streptococci, represents a technical improvement over the older method by eliminating spontaneous agglutination The second, the antihyaluronidase test, measures the inhibitory substance in human blood serum against bacterial hyaluronidases It is the purpose of this paper to report on clinical studies of these two relatively new techniques and to compare the results of these two tests simultaneously with those obtained by the better known antistreptolysin O and antistreptokinase tests

PATIENTS AND METHODS

The majority of patients in this study were seen on the medical wards and in the Arthritis Clinic of the New Haven Hospital Diagnoses were established on the basis of careful clinical observation of each patient sup-

* From the Section of Preventive Medicine, Yale University School of Medicine, New Haven, Connecticut This study was aided by a grant from the Life Insurance Medical Research Fund

† Milbank Memorial Fellow

plemented by roentgenologic and laboratory examinations of many of them These adult patients were arranged in the groups shown in Table 49 Blood specimens were collected and the serum separated and stored at —20° C. Each serum specimen was tested by means of four tests. Methods employed were as follows:

fied by Liao[5]

revention test described by McClean[7], the hyaluronidase was that elaborated by a strain of group A type 4 beta hemolytic streptococcus.

Table 49. Diagnoses and Number of Patients Studied

DIAGNOSIS	NUMBER OF PATIENTS
NORMAL SUBJECTS	53
UPPER RESPIRATORY beta HEMOLYTIC STREPTOCOCCAL INFECTIONS	33
RHEUMATIC FEVER, ACTIVE	68
RHEUMATIC FEVER, INACTIVE	64
RHEUMATOID ARTHRITIS	56
NON-RHEUMATOID ARTHRITIS (OSTEOARTHRITIS, GOUT, REITER'S SYNDROME TUBERCULOUS AND SYPHILITIC ARTHRITIS)	32
TOTAL	306

3 Antistreptolysin O—the method described by Todd[8] and modified by Hodge and Swift[9]

4. Antistreptokinase—the quantitative procedure described by Kaplan[10]

RESULTS

To provide a baseline the mean serum titers for each of the four antibodies were determined for normal subjects These are shown in Figure 111 along with the mean titers for each antibody for patients with inactive rheumatic fever and patients convalescent from beta hemolytic streptococcal infections of the upper respiratory tract. The mean titers and the frequency distribution for normal subjects were found to correspond with those for normal individuals reported from this laboratory and by others The agglutination titer and the two antienzyme titers, antihyaluronidase and antistreptolysin O, were significantly higher in these two groups of patients than those for normal subjects The antistreptokinase titers were identical in patients with inactive rheumatic fever and normal subjects but significantly higher in patients convalescent from streptococcal infections There were no significant differences in any of the antibody titers for pa- ... fever and streptococcal infections except in ... as much higher in the latter disease. ... the four antibodies for the groups of

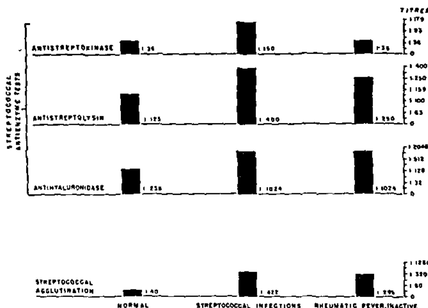


Fig 111 Antienzyme and streptococcal agglutination titers for normal subjects and patients with streptococcal infections and rheumatic fever (inactive)

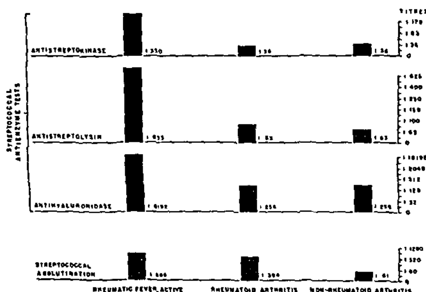


Fig 112 Antienzyme and streptococcal agglutination titers for patients with rheumatic fever (active), rheumatoid arthritis, and nonrheumatoid arthritis

patients with active rheumatic fever, rheumatoid arthritis, and nonrheumatoid forms of arthritis. In patients with active rheumatic fever the mean antienzyme titers were significantly higher than those for any other groups of patients studied The agglutination titer was not significantly higher than that found for patients with rheumatoid arthritis, inactive rheumatic fever or streptococcal infections but was markedly higher than in normal subjects The mean agglutination titer for the patients with rheumatoid arthritis was significantly higher than that for patients with nonrheumatoid forms of arthritis and normal subjects, but the antienzyme titers were nearly identical All four mean antibody titers were similar for patients with nonrheumatoid arthritis and normal subjects.

COMMENT

Figure 113 has been prepared to show the percentage of patients with active rheumatic fever, rheumatoid arthritis and nonrheumatoid arthritis

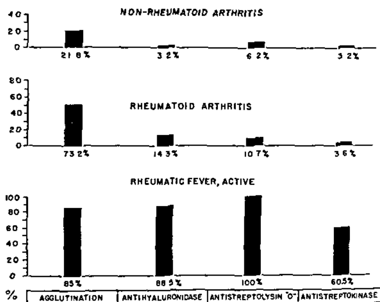


Fig 113 Percentage of patients with rheumatic fever (active), rheumatoid arthritis, and nonrheumatoid arthritis who had antienzyme and streptococcal agglutination titers above the usually accepted normal level

who had antibody titers above the usually accepted normal level All of the antibody titers were definitely elevated in over 85 per cent of the patients with active rheumatic fever, with the exception of antistreptokinase which was elevated in 60 per cent of these patients In the group of patients with rheumatoid arthritis the agglutination titer was elevated in 73 per cent, but the percentage with elevated antienzyme titers was very small, ranging from three to fourteen The percentage of patients with nonrheumatoid forms of arthritis who had antibody titers higher than normal was negligible These variations in streptococcal antibody patterns would suggest possible fundamental differences between these three disease processes,

i e., rheumatic fever, rheumatoid arthritis and nonrheumatoid forms of arthritis, although it is admitted that the number of observations is small

On the basis of these differences in antibody patterns, further clinical trial is warranted It would seem that the agglutination test employing autoclaved group A hemolytic streptococci might be used as a screening test to exclude the nonrheumatoid arthritides When the agglutination titer is high, then one of the antienzyme tests, preferably the antihyaluronidase for technical reasons, may be employed to differentiate between rheumatic fever and rheumatoid arthritis

One important point must be emphasized, namely, that a recent hemolytic streptococcal infection in a patient with arthritis may alter the antibody titers so that they would resemble those in patients convalescent from hemolytic streptococcal infections.

Table 50 Comparison of Antienzyme and Streptococcal Agglutination Titers between Patients with Rheumatic Fever (Active), Rheumatoid Arthritis and Nonrheumatoid Arthritis

TESTS	RHEUMATIC FEVER ACTIVE	RHEUMATOID ARTHRITIS	NON-RHEUMATOID ARTHRITIS
STREPTOCOCCAL ANTIENZYME TESTS	TITRES	TITRES	TITRES
1-ANTIHYALURONIDASE 2-ANTISTREPTOLYSIN "O" 3-ANTISTREPTOKINASE	HIGH	LOW	LOW
STREPTOCOCCAL AGGLUTINATION TEST WITH AUTOCLAVED BACTERIA	HIGH	HIGH	LOW

In summary (Table 50) if these tests should be used as aids in the dif-

titer would favor a diagnosis of active rheumatic fever Low antienzyme titers and a high agglutination titer would favor the diagnosis of rheumatoid arthritis, whereas low antienzyme and low agglutination titers would favor a diagnosis of one of the forms of nonrheumatoid arthritis.

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IMMUNOLOGIC REACTIONS IN RHEUMATOID ARTHRITIS*

R. H. BOOTS, M. O. LIPMAN, J. A. COSS, JR., AND CHARLES RAGAN

In our clinic, three immunologic tests—hemolytic streptococcus agglutination, differential sheep cell agglutination and determination of the antistreptolysin O titer—have been found useful from the viewpoint of differential diagnosis as well as prognosis of rheumatoid arthritis.

STREPTOCOCCUS AGGLUTINATION

Cecil, Nicholls and Stainsby[1] in 1930 reported that certain strains of streptococci were agglutinated to a high titer with sera of patients with rheumatoid arthritis Later, these strains were found to be group A hemolytic streptococci.[2] In general, we have followed the technique originally described by Nicholls and Stainsby.[3] In reading reactions, the character of the agglutination in the lower dilutions of sera has been found of greater significance than the titer.[4] A result is classified as "positive" only if the 1/20 dilution shows coarse, firm clumps with clear fluid between the clumps, "doubtful" indicates smaller clumps and cloudy fluid, "negative" designates no agglutination or fine granulation

ove, occurred with

This agglutination

ot non-type-specific

pneumococci[5] Absorption with strains of different group A types has removed the agglutinins for all types. Cross absorptions with a non-type-specific pneumococcus and with a group C strain of *Streptococcus hemolyticus* have resulted in a weakening but not a removal of the agglutinins

tion. The results of absorbing with the protein fraction K (Heidelberger) were also negative The agglutinins seem to be of the nature of true anti-

[illegible] in positive sera has been

ciation with strong salt solution

Wallis[7] made an interesting study of the agglutination phenomenon using fine collodion particles as well as the streptococcal organisms. Using the technique of Cannon and Marshall, he found that many rheumatoid arthritis sera agglutinate suspensions of these collodion particles. Because of this fact and the presence of feeble agglutinins for group A hemolytic streptococci in normal individuals, he postulated that the "increased ability of the sera of patients with rheumatoid (atrophic) arthritis to agglutinate selected strains of hemolytic streptococcus of group A is due to a nonspecific

Table 51 Agglutination of Group A Streptococcus and of Collodion Particles

	RHEUMATOID ARTHRITIS																		DEGEN. JOINT DISEASE	
Patient	Ma			Ru			Ro			Wa			Bi			Br			He	
Agglutinogen	1/20	Titer	Result	1/20	Titer	Result	1/20	Titer	Result	1/20	Titer	Result	1/20	Titer	Result	1/20	Titer	Result	1/20	Result
Whole broth culture	++±	640	Pos	++±	640	Pos	++	320	Pos	++	320	Pos	++±	160	Pos	++	160	Pos	0	Neg
Filtrate-coated collodion particles	++±	640	Pos	++±	1280	Pos	++±	160	Pos	++±	640	Pos	++±	640	Pos	++±	80	Pos	0	Neg.
Broth-coated collodion particles	+±	320	Doubt	+	640	Neg	+±	160	Doubt.	+±	320	Doubt	+±	160	Doubt	+±	320	Doubt	0	Neg
Collodion particles in 0.5% NaCl	+±	80	Doubt	+±	80	Doubt	+	20	Neg	+	20	Neg	+	20	Neg	+	40	Neg	0	Neg.
Washed streptococci in 0.5% NaCl	++	320	Pos	+±	160	Doubt	+±	320	Doubt	+±	160	Doubt	+±	160	Doubt	+±	160	Doubt	0	Neg

enhancement of the action of normally present agglutinins." We do not concur with Wallis' explanation but agree that it is possibly a nonspecific reaction.

We have compared the agglutinability of whole cultures with that of washed organisms from the same cultures as well as with filtrate-coated collodion particles. Table 51, showing the results of comparative tests with a few representative sera, illustrates our findings Collodion particles coated with the filtrate of an agglutinable culture have been agglutinated by many sera in a fashion similar to that of the whole culture, suggesting that the agglutinable factor is a product of group A streptococci Organisms washed from three to six times and resuspended in saline to the original volume have been agglutinated much less than the whole culture Few of the sera which are "positive" with a whole culture or with filtrate-coated collodion particles have agglutinated a saline or broth suspension of collodion particles to a significant degree Most of the sera tested against uncoated particles have given negative or equivocal reactions, different in character from the agglutination of whole culture or of filtrate-coated collodion particles. It would seem that three factors play a part in this agglutination· the serum containing the agglutinating property, a product of group A streptococci present in the filtrate, and the bacterial organisms The last can be replaced partially, at least, by inert substances such as collodion particles

The agglutination reaction of Cecil, Nicholls and Stainsby, which depends on the presence of a product of group A streptococci in a broth culture, is entirely different from that described by Quinn and Liao * The latter, following the technique of Thulin, used washed, autoclaved streptococci suspended in buffer solution Thulin[8] himself concluded "that the reactions with living streptococcal antigen . and the autoclaved antigen are of different character"

[illegible]

of [illegible]

cer [illegible]

matoid arthritis Subsequent follow-up has shown that a proportion of those patients whose disease was diagnosed clinically as rheumatoid arthritis, and who had a negative streptococcus agglutination, had rheumatic fever With one or two exceptions all patients with subcutaneous nodules have given a positive agglutination The agglutination has been positive less frequently in juvenile rheumatoid arthritis (10 per cent), rheumatoid arthritis of the spine (2 per cent), and rheumatoid arthritis with psoriasis (20 per cent)

The agglutination reaction of a patient changes infrequently except with chrysotherapy. We have had no opportunity to observe the effect of cortisone or the pituitary adrenocorticotrophic hormone on this agglutination

Of those patients followed more than five years (246 patients), 52 per cent had a negative or doubtful agglutination which remained negative or doubtful, 26 per cent had a positive reaction which remained positive, 3 per cent changed from negative to positive while under observation, and 19 per cent changed from positive to negative or doubtful (over two-thirds of these while receiving chrysotherapy). With this change in agglutination, the disease becomes inactive Few patients with diseases other than rheumatoid arthritis have been found to possess this agglutinating property

* See page 331

Positive reactions have been given by occasional patients with a streptococcal infection, rheumatic fever, scleroderma, periarteritis nodosa and disseminated lupus erythematosus. Occasionally a positive reaction occurred in a patient with skeletal pains but in whom we were unable to make a clinical diagnosis of rheumatoid arthritis.

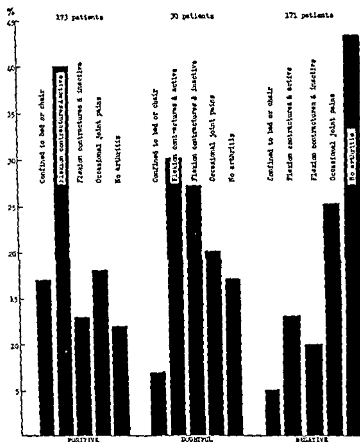


FIG 114 End result in 374 rheumatoid arthritis patients in relation to streptococcus agglutination

Our present viewpoint is that the mechanism of this agglutination and its significance in regard to the etiology of rheumatoid arthritis are still unknown. The reaction may be nonspecific, comparable to the Weil-Felix reaction. However, this does not minimize its practical value in diagnosis. In prognosis it is also of value since the presence of a positive streptococcus agglutination (Fig. 114) indicates a poorer prognosis than when the agglutination is negative.

ANTISTREPTOLYSIN O TITER

Todd[9] in 1932 showed that the antistreptolysin titer furnished an accurate method for determining the presence of recent infection with hemolytic

streptococci. Following such infections, the titer of antistreptolysin O rises rapidly, remains elevated for a variable number of months, and gradually tends to return to normal values. This test has been found of particular value in rheumatic fever and acute nephritis, where high titers are the rule. Rothbard and co-workers[10] have reported on the antibody response to the known antigenic components of group A hemolytic streptococci. These included the antistreptolysin O, antifibrinolysin, bacteriostatic and anti-M precipitin responses While from their study it was evident that at present

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s

an excellent antigen and the titer of its antibody can be accurately determined. Significant rises in this titer occurred in 77 per cent of persons with rheumatic fever in their series.

In 1936 it was reported from our clinic[11] that the antistreptolysin O titer is increased in many early cases of rheumatoid arthritis Most late cases showed a normal titer. In the subsequent thirteen years of follow-up this has not been corroborated. A majority of those early cases reported as having a high antistreptolysin O titer are now believed to have had rheumatic fever We have observed forty instances of such patients who clinically seemed to have had early rheumatoid arthritis with an elevated antistreptolysin O titer and who subsequently proved to have adult rheumatic fever. The salient characteristics of these cases are (1) a preceding history of an upper respiratory infection, (2) fusiform joint swellings simulating early rheumatoid arthritis, (3) complete recovery of the arthritis after weeks or months, (4) a response to salicylates much poorer than in typical rheumatic fever, (5) evidence of carditis more frequently than in rheumatoid arthritis, and (6) an elevated antistreptolysin O titer uniformly present.

We now believe that high titers do not occur in rheumatoid arthritis more frequently than in the general population A high titer is seldom accompanied by a positive agglutination reaction. A change in agglutinating power from negative to positive following an elevated antistreptolysin O titer has rarely been observed Certainly the results of antistreptolysin O determinations have failed to incriminate *Streptococcus hemolyticus* as an etiologic factor in rheumatoid arthritis.

SENSITIZED SHEEP CELL AGGLUTINATION

This differential agglutination test of sheep erythrocytes was recently

with the sera of patients having rheumatoid arthritis. The origin of these hemagglutinins in rheumatoid sera is not known Waaler[13] in 1939 had reported a peculiar activating effect upon agglutination of sensitized sheep blood cells by serum from various individuals, particularly those with rheumatoid arthritis. In a series of tests in collaboration with Dr Rose, a clinical correlation was found between this reaction and the streptococcus agglutination in that most patients with a ... had

a positive sensitized sheep cell ... ns

for these two reactions are distr ... ic

component, *since the agglutinins for the streptococcus can be absorbed* completely without decreasing the agglutinins for sensitized sheep cells No satisfactory explanation has been offered for this unusual finding of two [illegible] discussing the sen- [illegible]ated that it had all [illegible] of the heterophile type.

COMMENT

Using the two agglutination reactions, at least 70 to 75 per cent of patients with rheumatoid arthritis will show either a positive streptococcus agglutination, a positive sensitized sheep cell agglutination, or both (Table 52) Both of these tests have been performed this past year on all arthritis patients at the Presbyterian Hospital While their routine use is to be desired, it is realized that in most diagnostic laboratories the performance of both is not practical Which agglutination test, then, is to be preferred? The advantage of the sensitized sheep cell agglutination is its technical simplicity. Any laboratory which is equipped to do routine Wassermann

Table 52. Serologic Differentiation of Rheumatic Diseases

SEROLOGIC DETERMINATION	DEGENERATIVE JOINT DISEASE	RHEUMATOID ARTHRITIS	RHEUMATIC FEVER
Antistreptolysin titer	0	0	+
Streptococcus agglutination	0	+	0
Sheep cell agglutination	0	+	0

reactions can with little trouble set up this test The actual reading of the titers is not difficult The streptococcus agglutination test, on the other hand, is time-consuming and its usefulness depends on suitable cultures and on discrimination in reading reactions Strong positive reactions and complete negatives are recognized readily but to differentiate between a weak positive reaction and a doubtful, or between a weak doubtful and a negative, is sometimes difficult for even an experienced reader The personal equation is one of the factors in the performance of this test that make it impractical for diagnostic laboratories. If further reports confirm the results of Drs Rose and Ragan, we would favor the sensitized sheep cell agglutination as a routine procedure

Any clinician dealing with rheumatic diseases must frequently find instances where it is difficult to differentiate between rheumatic fever and rheumatoid arthritis, or between rheumatoid arthritis and degenerative joint disease In such cases he feels much more sure of his ground if he has the corroborative laboratory evidence of these serologic reactions.

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DISCUSSION

NANNA SVARTZ

First I should like to stress especially two of Dr Boots' important remarks on immunologic reactions in rheumatoid arthritis: (*a*) The significance of the streptococcal agglutinations in regard to the etiology of rheumatoid arthritis is still unknown, (*b*) the results of antistreptolysin O determinations have failed to incriminate *Streptococcus hemolyticus* as an etiologic factor of rheumatoid arthritis

Dr Boots further emphasized the fact that these two reactions are not specific for rheumatoid arthritis It is, therefore, of great importance that

Table 53 Absorption of Hemagglutinins by Normal Sheep Cells in Reiter's Disease

ERYTHROCYTES	BEFORE ABSORPTION Serum dilutions, 1 part in.							DIFFERENTIAL TITER	AFTER ABSORPTION Serum dilutions, 1 part in						
	4	8	16	32	64	128	256		4	8	16	32	64	128	256
Normal	3	2	1	1	0			1	0	0	0	0	0		
Sensitized	3	2	2	1	0				1	0	0	0	0		

the differential sheep cell agglutination test of Rose and associates, although apparently specific, has given positive results in only 30 to 40 per cent of cases of rheumatoid arthritis

While I was engaged in collaboration with Dr Schlossmann in trying out the differential agglutination test, we found an absorption test which, in the trials carried out so far, has given positive results in all cases of rheumatoid arthritis Something similar to this has also been reported by Sulkin and co-workers *

On sera from both healthy and sick persons we carried out different absorption experiments, using both sensitized and unsensitized sheep cells In the majority of the sera the hemagglutinins could easily be absorbed by normal sheep cells Thus, the sheep cell agglutination test carried out on the centrifuge fluid gave a negative result, whether the reaction was made with unsensitized or sensitized red blood corpuscles Table 53 shows an example of this. However, sera from rheumatoid arthritis patients reacted in an entirely different way If absorption experiments with normal sheep cells were made on sera from patients suffering from rheumatoid arthritis and the sheep cell agglutination test was then made on the supernatant fluid, the following results were obtained

As with all other sera, the reaction was negative if unsensitized sheep cells were used, but sheep cell agglutination carried out with sensitized

* See p 360

Table 54 Absorption of Agglutinins by Normal Sheep Erythrocytes in Cases of Rheumatoid Arthritis

PATIENT	ERYTHROCYTES	HEMAGGLUTINATION BEFORE ABSORPTION Serum dilutions, 1 part in											DIFFERENTIAL TITER	HEMAGGLUTINATION AFTER ABSORPTION Serum dilutions, 1 part in										
		4	8	16	32	64	128	256	512	1024	2048	4096		4	8	16	32	64	128	256	512	1024	2048	4096
L. O	Normal	3	3	2	2	1	0	0	0	0			8	0	0	0	0	0	0	0	0	0	0	
	Sensitized	3	3	3	2	2	2	1	1	0				4	4	4	3	3	2	2	1	1	0	
S. P	Normal	3	3	3	3	2	1	0	0	0	0	0	16	0	0	0	0	0	0	0	0	0	0	
	Sensitized	4	4	4	4	4	3	3	2	2	1	0		4	4	3	3	3	2	1	1	1	1	
M. F., absorbed once	Normal	2	2	2	0	0	0	0	0	0	0		64	0	0	0	0	0	0	0	0	0		
	Sensitized	3	2	2	2	2	1	1	1	1	0	0		3	3	3	3	2	2	2	1	0		
M. F., absorbed twice	Normal	2	2	2	0	0	0	0	0	0	0		64	0	0	0	0	0	0	0	0	0		
	Sensitized	3	2	2	2	2	1	1	1	1	0			3	3	2	2	2	2	2	1	0		

sheep cells was not affected by a preceding absorption with normal sheep cells In all tests so far carried out (about fifty) on sera from patients with rheumatoid arthritis the results have been the same. Table 54 shows some of these results Strikingly enough, no other disease has, so far, shown these results in absorption tests. A slight agglutination sometimes remains when the test is made with sensitized sheep cells. This agglutination can always be induced to disappear after one more absorption. It is quite probable, of course, that other diseases will be found which give the same reaction With the experience that we have already gained in regard to the outcome of the absorption reaction in, for instance, different articular diseases, it is not very likely that this will have much effect on the usefulness of the

Table 55 Sheep Cell Agglutination in Serum of Rabbits Injected with Enterococci

RABBIT	STRAIN	BLOOD DRAWN AFTER	JOINT AFFECTION	SHEEP CELLS	AGGLUTINATION TITER FOR SHEEP CELLS		AGGLUTINATION TITER FOR ENTEROCOCCI
					BEFORE INJECTION	AFTER INJECTION	
8	8Ws	4 days	+	Normal	1·16	1·1024	1 7000
				Sensitized	1 32	1 2048	
16	8Wf	4 days	+	Normal	1 16	1 2048	1 7000
				Sensitized	1 32	1 2048	
19	Vaccine 80°8Ws	6 days	0	Normal	1 32	1 64	1 5400
				Sensitized	1 64	1 64	
20	Seitz filtrate 8Ws	7 days	0	Normal	1 16	1 16	1 40
				Sensitized	1 16	1 16	

test We were able, with the aid of Meyer's method (1922), to absorb even the reaction carried out with sensitized red blood corpuscles in cases of rheumatoid arthritis.

Schlossmann and I have made further experiments on the theoretical aspect of sheep cell agglutination We decided to carry out experiments on animals with a view to ascertaining what bearing (if any) the infection has on that form of hemagglutination which is being discussed here. Since I have found enterococci particularly useful for inducing both acute and chronic arthritis, these bacteria were chosen first for our experiments. The remarkable and, so far as we could ascertain, the hitherto unknown fact, could be demonstrated that enterococci are capable of inducing antisheep-cell agglutinins. All strains of enterococci so far tested on rabbits have thus given rise to sheep cell agglutinins in serum. These hemagglutinins are not absorbed by the bacteria which induced them (see Table 55).

Subsequently, other bacteria have been tested, the experiments with streptococci being, of course, of the greatest interest. Neither *S. viridans* nor beta hemolytic streptococci have given rise to sheep cell agglutinins (Table 56) It is worthy of especial mention that a *strain of hemolytic* streptococci which had been obtained from the State Serum Institute in Copenhagen, and which is generally used in Scandinavia for the purpose [illegible] rheumatoid arthritis, for instance,
[illegible] cci and

Besides enterococci, we have found, in collaboration with Olhagen, that certain strains of pneumococci are capable of forming hemagglutinins. However, this reaction has been very weak except in the case of Type 42, which, upon being injected into rabbits, induced the formation of hemagglutinin in the same way as enterococci.

*Table 56. Agglutinins against Sheep Cells in Serum from Rabbits Injected with Bacteria other than Enterococci**

BACTERIA	AGGLUTINATION TITER FOR BACTERIA
Streptococcus, S.F. 130, Group A, Type 1	1:280
Streptococcus, Group A	1:250
Streptococcus, Group A, Type 14	1:200
Streptococcus viridans	1:200
Staphylococcus aureus	1:600
Salmonella typhosa	1:280
Pneumococcus, Type 3	1:800
Pneumococcus, Type 42	1:2000

* Agglutination titers for sheep cells were 1:16 and 1:32 in all cases (normal agglutination in rabbits up to 1:64), except that titers up to 1:128 were used with Type 42 pneumococcus.

The sheep cell agglutination obtained from the rabbits infected with enterococci could usually be suppressed if the serum had been adsorbed in advance with normal sheep blood corpuscles. However, in one of the animals in which enterococci were injected in October, 1948, and which exhibits symptoms of chronic arthritis, we have succeeded in showing a reaction that is identical to that observable in rheumatoid arthritis. Three earlier tests were negative.

° ° °

BLOOD SLUDGE IN PATIENTS WITH ARTHRITIS*

I. A Preliminary Report

MARJORIE B. PATTERSON AND RICHARD H. FREYBERG

Blood sludge is the intravascular agglutination or clumping of red blood cells into masses, due to the deposit of a sticky material which forms a coating on the surface of the erythrocytes and causes them to adhere to each other. Cells in sluggish masses change normal blood into circulating sludge. These changes have been observed following trauma or injury, and in many diseases.

The purpose of this paper is to report a study of blood sludge in patients with arthritis, aimed to determine (*a*) the incidence and characteristics of blood sludge in various types of arthritis, (*b*) whether there is correlation between the character of the sludge and different structural stages, or the degree of rheumatoid activity; (*c*) how sludge influences the pathologic physiology of rheumatoid arthritis, and (*d*) if the sludging process lessens coincident with clinical improvement

PREVIOUS OBSERVATIONS OF BLOOD FLOW IN PATIENTS WITH ARTHRITIS

In patients with rheumatoid arthritis, changes have been seen in smaller vessels of the peripheral circulation Kovacs, Wright and Duryee[1] noted the high incidence of constriction of the capillaries, slowing of the rate of flow, and sometimes an interrupted capillary flow in patients with rheumatoid arthritis In both rheumatoid arthritis and osteoarthritis these changes were associated with lowered surface temperature, measured at the fingernail fold Pemberton[2] also reported that such abnormalities occurred in 75 per cent of arthritic subjects. Knisely et al[3, 4] mentioned *the occurrence of sludge in 125 patients with rheumatoid arthritis*, but reported no details.

CRITERIA OF NORMAL BLOOD FLOW AND PROPERTIES OF SLUDGED BLOOD

The criteria of normal blood flow, the properties of sludged blood and the effects of damaged leaking vessels in man, have been described in detail by Knisely et al[4] and are reiterated here in brief form, in order to elucidate the method of this study and the appraisal of the circulation in patients with arthritis.

vessels.

4. Flow in 60- to 100-micron vessels is so rapid that individual red blood cells cannot be seen.

Circulating Sludge 1. Coated erythrocytes form clumps varying in size and shape, plasticity or rigidity, elasticity, fragility or toughness, and with different surface characteristics In arterioles such masses which do not break up as they pass to capillaries are called "basic masses." Agglomerates in venules are composed of basic masses

2 Leukocytes adhere to the endothelial linings of vessels.

3 Coated erythrocytes are phagocytized by reticuloendothelial cells of the liver, spleen and bone marrow, thus removing considerable numbers of red blood cells from the circulation and contributing to reduced cell volume *and anemia.*

4 ... reduce the ... to ... rate ... of ... tissue ... vessel walls so that plasma leaks into tissues Edema occurs in perivascular tissues when the rate of *leaking exceeds the capacity of* lymphatic return

5. Leaking and plasma loss contribute to lowered circulating blood volume and to hemoconcentration These changes, together with retarded blood flow, permit settling or sedimentation of sticky red cell masses from the plasma, and the formation of temporary or permanent thrombi.

6 Decrease in circulating blood volume caused by plasma loss and by phagocytosis of coated erythrocytes may initiate temporary or prolonged constriction of conjunctival arterioles and capillaries

METHODS

Microscopic observations of flowing blood and of vessel walls in patients were made by use of the Knisely technique,* employing a stereoscopic microscope focused on the obliquely illuminated bulbar conjunctiva

Ninety patients were observed The group comprised sixty cases of rheumatoid arthritis, fourteen patients with rheumatoid spondylitis seven of whom had no peripheral joint involvement, ten cases of osteoarthritis, and four cases of gouty arthritis

Sludge was studied in relation to the age of the patient, the duration of the disease, the stage of structural changes, and the disease activity In most instances examinations for the presence of sludged blood were made before therapy was instituted by us, although a few patients were receiving small doses of acetylsalicylic acid for analgesia Subsequent observations were made at intervals during treatment and during clinical improvement in some patients

Ten patients received 50 mg of gold thioglucose weekly until 1000 mg had been given, and thereafter 25 mg once or twice a month as a maintenance dose until rheumatoid activity subsided Two rheumatoid subjects were treated intravenously with copper salts in doses of 500 mg twice a week until 4 gm were given A similar series of injections was repeated after an interval of one month Two patients with rheumatoid spondylitis received roentgen therapy to the back through one or more ports in total doses of 600 r through each portal in each of two courses of treatment

To determine whether blood sludge would be lessened by the use of quinine sulfate, three rheumatoid patients were given 0 6 gm to 2 0 gm daily over periods varying from two and one-half to four months

Estimation of anemia was made on samples of venous blood by determination of the mean corpuscular hemoglobin concentration This calculation was based upon hemoglobin values (Sahli method) and the volume of packed red blood cells per 100 ml of blood (hematocrit) by Wintrobe's procedure

RESULTS

Some degree of blood sludge was observed in all patients with arthritis
Eighty-three per cent of the patients with rheumatoid arthritis showing
pronounced blood sludge had a moderately severe or severe degree of rheu-
matoid activity and structural changes stages II III or IV (Therapeutic
Criteria,* American Rheumatic Association) The character of the sludg
present bore no constant relation to the age of the patient, nor to the tot
duration of the disease A potentially more harmful sludge was present
onset of the disease or with exacerbation or recurrence Rigid basic clum
acting as minute emboli intermittently or permanently plugging termi
arteriole tips the "bottleneck of the circulation" were seen during the
periods of rheumatoid activity Large tenacious agglomerates which br
up with difficulty at venule bifurcations and which retarded rates of f
were also present Seventy-five to 100 per cent of the red cells were co

* See p 12

and were clumped in the circulation. When such sludge persisted for a length of time, there was a direct correlation with a high degree of rheumatoid activity.

[illegible]

sider that this would be an important handicap to recovery A significant degree of blood sludge was present in all patients with an elevated erythrocyte sedimentation rate.

Thirty per cent of thirty-nine patients with rheumatoid arthritis who were examined for anemia showed subnormal mean corpuscular hemoglobin concentration concomitant with severe or moderately severe blood sludge and a high degree of rheumatoid activity. The patients in this group (70 per cent) who had normal mean corpuscular hemoglobin concentration had a similar degree of blood sludge and clinical activity was present.

Four patients who responded to treatment so that rheumatoid activity showed major improvement (grade II, Therapeutic Criteria)* and in whom this improvement was maintained for four to six months, showed persistence of sludge, indicating that sludge does not quickly reverse in this period of time. However, the character of the sludge differed from that seen at the time of clinical activity, in that the agglutinated masses were smaller, softer, less numerous, and blood flow rates were less retarded The character of the sludge seen in three patients examined while in remission, considered grade II at the time of first sludge examination, was similar to that observed in the patients who, under treatment, had reached grade II improvement

Changes in the blood sludge were observed in one rheumatoid patient who received cortisone for twenty-three consecutive days. On the fourth day after injections were begun there was an increase in the circulation rate, agglomerates became smaller and softer, and hard basic masses present before the use of cortisone, became smaller and less rigid, intermittently plugging terminal arteriole tips for shorter periods. After the eighth day of observation basic masses again became rigid and remained relatively hard until the forty-second day Other characteristics of the sludge varied during this interval, being interpreted as improvement or regression Maximum improvement in the sludge did not appear until the forty-second day of observation, eighteen days after withdrawal of cortisone Slight regression from this peak of improvement in the blood sludge occurred in the subsequent four weeks, but the potentially damaging factors present before the use of cortisone had not returned at the time of presentation of this report, ten weeks after injections began The unsludging lagged behind the decline of the erythrocyte sedimentation rate and even further behind the rate and degree of clinical improvement. Seven weeks after stopping cortisone the patient showed early symptoms of clinical regression and the erythrocyte sedimentation rate had returned to 101 mm per hour, yet the improvement in blood sludge was maintained at slightly less than maximum. In this patient, regression in the blood sludge picture did not parallel the rise in sedimentation rate nor the early clinical regression.

In 70 per cent of the patients receiving chrysotherapy the sludge worsened after 225 to 1000 mm of gold thioglucose had been given, even after a grade II or III response to therapy This sludge was characterized by

* See p 12

more rigid basic masses which intermittently plugged terminal arteriole tips and reduced flow rates to zero in these vessels for a few seconds. Agglomerates in the venules were, in general, larger, tougher, and broke up with difficulty. Venous flow rates were further retarded. Vessel wall damage was evident in increased leaking of plasma fluids and bulging of arterioles or sacculation of venules. All cells were coated.

No significant changes in the character of the sludge were observed in two patients treated intravenously with copper salts, although one person showed slight clinical improvement (grade III).

Sludge improved slightly coincident with quinine therapy. There were fewer clumped erythrocytes, the masses were smaller and softer, and blood flow rates increased or became nearly normal. With discontinuance of the drug, this improvement was not maintained.

In the patients with rheumatoid spondylitis, with or without involvement of joints in extremities, the degree of sludge correlated directly with activity of the disease. Considerable reversal of the sludging process and symptomatic relief was observed in two spondylitic patients without peripheral joint disease after two courses of roentgen therapy to the back. The agglutinated masses became smaller, circulation rates improved, and with better oxygenation, leaking through vessel walls lessened.

Although all patients with osteoarthritis showed sludged blood, in general it was less severe than in rheumatoid subjects. Rigid basic masses were seldom seen, and the intravascular pathology was considered less damaging.

Blood sludge was pronounced in four patients with gouty arthritis. Hard basic masses acting as emboli were seen in terminal arteriole tips, temporarily reducing arteriole flow rates to zero. Conjunctival vessels appeared to show lowered blood volume and arterioles were constricted. All cells were coated and vessel wall damage was evident. The findings present in acute attacks were not significantly lessened during the intervals between attacks of gouty arthritis.

COMMENT

To what degree sludged blood affects the signs and symptoms or contributes to the abnormal physiology of rheumatoid arthritis is not precisely known, but the process and its effects are somewhat revealed by clinical and microscopic observations. Prolonged generalized sludging may cause macroscopic edema and hypertrophy of the vessels of the bulbar conjunctiva. The cold extremities attributed to peripheral vasoconstriction in certain phases of rheumatoid arthritis may be related, in part, to the physiologic compensatory constriction of the peripheral bed as a result of persistent blood sludge for a time sufficient to damage vessel walls to the point of leaking, with partial plasma fluid loss and lowered blood volume. If postcapillary venules in the joint capsule are damaged by anoxia caused by prolonged sludging, the leaking of plasma may contribute to joint effusion. More facts need to be known before it can be said that the altered physiology of the circulation produced by sludging adversely affects the local tissue defense in the joints and/or the body's normal immunologic response against disease and thereby handicaps recovery.

No attempt has been made to classify the kinds of sludge present in patients with arthritis. Our experience is insufficient to enable us to evaluate all the variables which may occur, so that attempts at precise grouping at

this time seem unwise. We do not know all the possible intravascular or vessel wall changes associated with different stages of structural change through which patients with rheumatoid arthritis may pass, nor do we yet know the relation of these vascular changes to various degrees of rheumatoid activity One can, however, estimate potential damage to peripheral vascular channels and to tissues supplied by them, and the possible pathologic physiology of the circulation which may result. Repeated showers of rigid basic masses, acting as temporary or permanent emboli in terminal arteriole tips, deprive the tissues supplied by these vessels of oxygen and nutrients Any therapy which would reverse the blood sludge and its deleterious effects upon the circulation might make more discernible some of the fundamental factors in rheumatoid arthritis

It was shown[5] that quinine caused unsludging or breaking up of large masses of coated agglutinated red cells in rhesus monkeys with *knowlesi* malaria. Whether this was due to decrease in the internal cohesion of the masses or to solubility of the coating on the red blood cells comprising the masses is not known. Although human blood proteins from which it is believed the coatings are derived are not identical with the blood proteins of the monkey, a trial of quinine as a possible means of reversing sludge in arthritis seemed indicated Our results with this drug suggest that it is effective in patients only while being administered, and has no lasting effect in reversing sludge, however, the number of patients is at this time too small to allow dependable evaluation

Unsludging occurred more rapidly and to a greater degree in the patient to whom cortisone was given than in any other patient. If further experience with cortisone proves its effectiveness in reversing the pathologic physiology of rheumatoid arthritis, blood sludge may be expected to lessen or be reversed whenever significant clinical improvement occurs with this hormone. Studies of these effects are being continued.

The effect of gold salts on the intravascular changes which occur during therapy cannot be fully evaluated from this limited study. Evidence is not available to indicate whether gold per se contributed to the changes observed, or whether they may be attributed entirely to alterations in the disease process, related or unrelated to this therapy.

How great a role is played by the reticuloendothelial cell phagocytosis of coated erythrocytes in sludged blood is not known It may be that the anemia observed in 30 per cent of our patients with severe blood sludge was due, in part, to removal of coated red cells by phagocytosis The normal mean corpuscular hemoglobin concentration values obtained in the remaining 70 per cent of patients studied for anemia was unexpected, in view of the severe blood sludge associated with their disease. Rapid ingestion and destruction of coated blood walls by phagocytes of the liver and spleen have been seen[5, 6] by the quartz rod method of in vivo observation when sludge was experimentally produced in animals. It is reasonable to assume that a similar process of phagocytosis would occur in rheumatoid patients whose blood contained a high percentage of coated erythrocytes However, this postulated removal of coated red cells from the circulation is not consistent with the normal or high hemoglobin and hematocrit values in 70 per cent of our patients Hemoconcentration resulting from loss of plasma fluids, which was observed in these patients, may have masked an anemia determined by the mean corpuscular hemoglobin concentration

With continued severe rheumatoid activity and associated blood sludging

phagocytosis No measurements of circulating blood volume have been made in our patients. If such a theory is substantiated by fact, to blood

systemic nature of the disease

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IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN, WITH SPECIAL REFERENCE TO RHEUMATIC FEVER*

VII. Inhibition of Hyaluronidase by Sera

NATHAN EPSTEIN, PAUL F. DE GARA AND MAY G. WILSON

The following study is one of a series of immunologic and biochemical pilot studies in children undertaken to obtain information as to the possible inherent differences in children susceptible to rheumatic fever This working hypothesis is based on the evidence previously presented that genetic susceptibility of the host is an important factor in the acquisition of this disease It is also well known that specific enzyme reactions may be influenced by genetic factors

The nature of the process responsible for the characteristic connective tissue changes in rheumatic fever is obscure Recent studies have implicated the hyaluronic acid–hyaluronidase enzyme system Investigations have been concerned with the inhibition of hyaluronidase by sera from patients with acute rheumatic fever It has been reported that streptococcal hyaluronidase activity is more markedly inhibited by sera from rheumatic patients than by sera of nonrheumatic controls

* From the New York Hospital and the Department of Pediatrics, Cornell University Medical College These studies were aided by grants from The Commonwealth Fund and The Helen Hay Whitney Foundation

MATERIALS

During the past four years we have collected about 900 blood specimens from normal, susceptible, and rheumatic children who are under our medical supervision. The specimens were stored at −20° C. Of these, 101 specimens of sera from children aged three to fifteen years were arbitrarily selected for this investigation. The turbidity method described by Dorfman was followed, with slight modifications Hyaluronic acid from human umbilical cord, and bovine testicular hyaluronidase (150 turbidity units per mg) were obtained from Dr. R McCullagh of Schering Laboratories

RESULTS

The results presented are expressed as the percentage reduction in enzyme activity of a standard solution of hyaluronidase (7.5 to 9 TRU per deter-

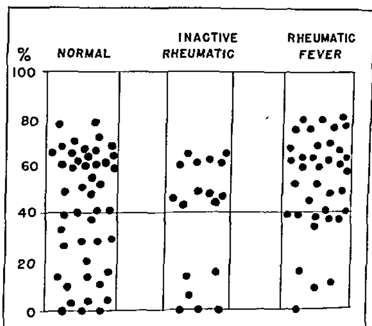


Fig 115 Distributions of percentage reduction of hyaluronidase activity by sera from normal children, from patients with inactive rheumatic fever and from children with acute rheumatic fever.

... of comparison values are given

In the sera tested, the degree of inhibition was not affected by ... age differences. The percentage reduction by sera from normal and susceptible children was within the same range.

... of the percentage reduction by sera from normal children ... fever and children with acute rheu- ... Figure 115. It is apparent that the distribution of values covers a wide range from 0 to 80 per cent. There is no significant difference in the degree of inhibition of hyaluronidase activ-

ity by the sera of children in each group. In the normal and inactive rheumatic series including sixty-four sera, 61 per cent showed a reduction greater than 40 per cent, compared to 73 per cent for thirty-seven sera *from children with acute rheumatic fever.*

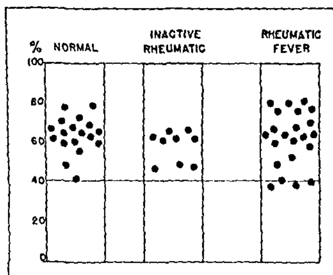


Fig 116 Reduction of hyaluronidase activity following antecedent respiratory illness

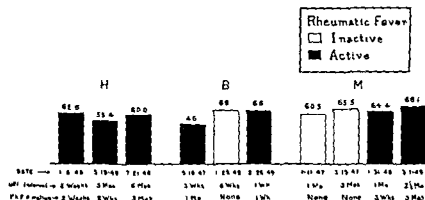


Fig 117 Results of serial determinations of hyaluronidase inhibition for three rheumatic children.

In previous studies of immunologic reactions among these patients it was observed that antistreptolysin titers, streptococcal agglutinin titers, and the gamma globulin component determined by electrophoresis were increased in patients who had experienced an antecedent respiratory illness presumably streptococcal in origin This was true irrespective of the presence or absence of rheumatic fever The data obtained were therefore analyzed with respect to the presence of antecedent illness. It may be seen in the

accompanying graph (Fig 116) that 95 to 100 per cent of the sera tested in each group gave a reduction of hyaluronidase activity greater than 40 *per cent.*

It was found that in the sera of fifty-two children without a recorded antecedent illness, 36 per cent showed a reduction greater than 40 per cent, in contrast to 96 per cent for forty-nine children with a recorded antecedent respiratory illness In the majority of the sera tested, respiratory illness occurred within one month In some instances reduction of hyaluronidase activity was noted six to eight months following an antecedent illness

The significance of antecedent respiratory illness is further demonstrated in serial determinations of hyaluronidase inhibition. Figure 117 shows that for three rheumatic patients, all of whom had had respiratory illness at intervals from two weeks to six months previously, the percentage reduction of hyaluronidase activity was not significantly different during the active or inactive phases of rheumatic fever.

COMMENT

It is apparent from these observations that the inhibition of this enzyme system by sera from rheumatic patients is not a reflection of the rheumatic process

The serum constituent responsible appears to be increased following antecedent respiratory illness presumably streptococcal in origin The observation of marked inhibition of bovine hyaluronidase by sera from children who have had an antecedent respiratory infection has also been reported for streptococcal hyaluronidase. It has been suggested that the inhibition observed is probably the reflection of an immunologic reaction

This view would receive support from the fact that in our series other serologic evidence of streptococcal infection was obtained for sera which showed marked inhibition of hyaluronidase activity. Further support of this concept is also given by the fact that the serum constituent responsible for decreasing the activity of the bovine enzyme was found to be heat stable. It has also been reported that the inhibitor of streptococcal hyaluronidase is heat stable

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TOXINS AND ENZYMES OF STREPTOCOCCI*

ALAN W. BERNHEIMER

With the growing belief in a causal relationship between streptococcal infection and rheumatic fever, there has developed an intensified interest in the composition and activities of the streptococcal cell. It has been known for many years that *group A streptococci possess the capacity* to elaborate during growth a variety of toxic products, but only in the last [illegible] directed toward the isola- [illegible] which [illegible] ed are

* From the Department of Microbiology, New York University College of Medicine and College of Dentistry, New York, N. Y.

soluble substances of high molecular weight, possessing the properties of proteins They are recognized almost exclusively by the biologic or biochemical effects which they bring about, the effects in each instance being relatively specific for the particular streptococcal product involved.

Group A streptococci (*Streptococcus pyogenes*) are capable of producing at least eight substances, each of which induces a specific alteration in mammalian cells or in chemical constituents thereof. These substances are streptolysin O, streptolysin S, scarlatinal (erythrogenic) toxin, proteinase, streptokinase, hyaluronidase, desoxyribonuclease and ribonuclease Every strain of group A streptococcus does not form all of these substances In fact, there exists among different strains a wide variation in regard to their

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TOXINS

Hemolysis is the oldest and one of the best known of the many possible types of activities possessed by streptococcal cultures and their filtrates Although numerous contradictory findings concerning the properties and production of the substance thought to be responsible for lysis exist in the literature of a few decades ago, the confusion largely disappeared with the demonstration[1] that many strains are capable of elaborating not one but two hemolysins These substances have been designated streptolysin O and streptolysin S,[1] O indicating reversible lability to oxygen and S standing for serum which favors the formation of streptolysin S Since their recognition a great many differences between the two lysins have been demonstrated, these include differences in chemical properties, in antigenic specificity and in the kinetics of lysis induced by the two agents There cannot therefore be any doubt about the existence of two distinct streptolysins It has been shown, moreover, that some strains of streptococci produce both toxins and that other strains produce either one or the other but not both[2] The variation in capacity of strains of group A streptococci to produce the two streptolysins has not been correlated with differences in the clinical severity of streptococcal infections or their sequelae

Streptolysin O Although streptolysin O and related toxins have frequently been studied in connection with their action on blood cells, they have been investigated less thoroughly in regard to possible biologic effects on cells other than erythrocytes and leukocytes Experiments utilizing the isolated frog's heart have recently demonstrated unique effects of streptolysin O and have shown in addition that the action of this toxin is by no means limited to the cells of the blood[3, 4, 5]

Application to the isolated frog's heart of a diluted solution of partially purified streptolysin O, previously activated with cysteine, produces little or no change in the heart beats as recorded kymographically The same is true even when a relatively large dose of streptolysin O is used, this may be contrasted with the action of other cardiotoxic agents such as the toxin of *Clostridium septicum* which acts in a single dose If the first dose of streptolysin O is now washed out of the heart and a second dose applied the heart undergoes systolic contracture It can readily be shown that the effect is not a result of a summation of the two doses

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This view would receive support from the fact that in our series other serologic evidence of streptococcal infection was obtained for sera which showed marked inhibition of hyaluronidase activity. Further support of this concept is also given by the fact that the serum constituent responsible for decreasing the activity of the bovine enzyme was found to be heat stable. It has also been reported that the inhibitor of streptococcal hyaluronidase is heat stable

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Hemolysis is the oldest and one of the best known of the many possible types of activities possessed by streptococcal cultures and their filtrates Although numerous contradictory findings concerning the properties and production of the substance thought to be responsible for lysis exist in the literature of a few decades ago, the confusion largely disappeared with the demonstration[1] that many strains are capable of elaborating not one but two hemolysins These substances have been designated streptolysin O and streptolysin S,[1] O indicating reversible lability to oxygen and S standing for serum which favors the formation of streptolysin S Since their recognition a great many differences between the two lysins have been demonstrated, these include differences in chemical properties, in antigenic specificity and in the kinetics of lysis induced by the two agents There cannot therefore be any doubt about the existence of two distinct streptolysins It has been shown, moreover, that some strains of streptococci produce both toxins and that other strains produce either one or the other but not both[2] The variation in capacity of strains of group A streptococci to produce the two streptolysins has not been correlated with differences in the clinical severity of streptococcal infections or their sequelae

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Instead, the first dose alters the reactivity of the heart so that the organ becomes highly sensitive to the second application of streptolysin O. The sensitivity of the heart has been shown to be due to the loss from the heart tissue of a protective substance or toxin inhibitor. The inhibitor is released on the first exposure of the heart to streptolysin O, and is removed in the perfusing fluid when the heart is washed prior to a second application of the toxin The release of inhibitor appears to be a specific and unique effect of streptolysin O, for other cardiotoxic agents which have been tested fail to exhibit a comparable effect. It would be most desirable to know the chemical identity of the inhibitor because such information may well provide an insight into the chemical nature of the cellular alteration which is initiated by the toxin. It is of interest to note that the inhibitor not only prevents the contracturing action of streptolysin O but also inhibits the lethal effect of streptolysin O injected intravenously into mice.

Whether or not a comparable mechanism exists in mammals is not fully established, but there are observations on record which are consistent with the view that streptolysin O affects mammalian tissue in a manner fundamentally similar to that of the frog's heart. Intravenous injection of a barely sublethal dose of streptolysin O causes mice to become partially resistant to a subsequently injected lethal dose The refractoriness develops within six hours following the sublethal dose and disappears in approximately forty hours. The refractory state depends not upon antibody formation but upon some other mechanism Investigation of the specificity of the induced resistance to streptolysin O has shown that the refractory mice are not in general resistant to other toxic substances whose pharmacologic effects resemble, more or less, those of streptolysin O An important exception to this generalization is provided by saponin Mice which have been injected with a sublethal dose of streptolysin O develop refractoriness not only to the streptococcal product but also to saponin Likewise, mice injected with a barely sublethal dose of saponin develop resistance not only to saponin but also to streptolysin O The unexpected reciprocal relationship suggests that there are fundamental elements of similarity in the modes of action of the two substances In order to investigate this point further the effects of the two substances on the isolated frog's heart were re-examined.[6] Analysis of the experimental results suggested that the ultimate site of cardiotoxic action of saponin and streptolysin O is normally covered by two barriers; one of these barriers is displaced by saponin, the other by streptolysin O Removal or displacement of either barrier permits either cardiotoxic agent to induce systolic contracture.

What implications the foregoing observations may have for an understanding of rheumatic processes is not entirely clear. Rheumatic patients possess much larger amounts of circulating antistreptolysin O than do persons who do not have rheumatism As the antibody represents a specific [illegible] of streptolysin O by the infecting [illegible] toxicity [illegible] ed toxin [illegible] could reach tissues remote from the site of local streptococcal infection.

Streptolysin S The biologic effects of streptolysin S have been investigated less thoroughly than those of streptolysin O and the chemical nature of the former has not been convincingly elucidated. A discovery of considerable interest is the finding that ribonucleic acid, or a fraction thereof,

specifically induces the formation by streptococci of streptolysin S.[7,8] As yet there is little information concerning the manner in which ribonucleic acid, or its active fraction, exercises this effect. Infecting cocci may make use of ribonucleic acid existing in or derived from the host cells, in producing streptolysin S during the course of a streptococcal infection. Although human sera possess the capacity to prevent hemolysis induced by streptolysin S, it has not been established that the inhibitory property of sera is due to a specific antibody. It has been reported[9] that the streptolysin S-inhibiting capacity of sera of rheumatic children is lower during periods of acute attacks than it is during nonrheumatic periods This finding stands in sharp contrast with that concerning antistreptolysin O and antistreptokinase the serum titers of which, during rheumatic activity, are usually markedly elevated.

The desirability of employing for experimental work *purified* streptococcal products is obvious to anyone who has read critically even a small part of the extensive literature on the biologic effects of culture filtrates Although the isolation of labile toxins and enzymes, present frequently only in minute amounts, presents technical difficulties, considerable progress has been made. Methods for obtaining highly potent preparations of streptolysin O,[10,11] streptolysin S[12] and streptokinase[13,14] have been described and erythrogenic toxin has been isolated in partially pure form[15,16,17] In addition, the quantitative aspects of the reaction of erythrogenic toxin with antitoxin have been investigated using the precise methods of immunochemistry.[15]

ENZYMES

Ever since the discovery[18] that cultures or culture filtrates of streptococci cause the lysis of human fibrin clots, there has been much interest in the phenomenon of streptococcal fibrinolysis both from the point of view of its mechanism and in regard to its significance in the pathogenesis of streptococcal diseases. It was early recognized that, unlike human fibrin clots, the fibrin clots of various species of animals frequently were partially or completely resistant to lysis.[18,19,20] It was further recognized that the differences in susceptibility of fibrin clots derived from different species of plasma were not due to insusceptibility of the fibrin itself but to some other factor. Further work[21] showed that a "lysin factor" present in the water-insoluble globulin fraction of human serum, distinct from fibrinogen and thrombin, was necessary for lysis to occur

Streptokinase. The mechanism of streptococcal fibrinolysis has to a large extent been elucidated by the finding that "lysin factor" is identical with a proteolytic enzyme-precursor (plasminogen) normally present in human plasma.[13,22,23] It has been established that fibrinolysin does not directl affect fibrin, but instead, catalytically activates plasminogen thereby co verting it to an active proteolytic enzyme (plasmin) Plasmin digests fibr clots and is capable also of digesting other proteins such as gelatin a casein In the light of this knowledge "streptococcal fibrinolysin" has b replaced by the term "streptokinase"[22]

In addition to the components of the fibrinolytic system just menti and to antistreptokinase, there is present in normal sera a substance w inhibits the proteolytic action of plasmin, and which is designated " inhibitor." Removal of serum inhibitor causes the conversion of plasm

jects display a higher average antibody response than do normal individuals to antigenic stimuli of other kinds. However, the observation serves to maintain interest in the possibility that an antigen-antibody mechanism may play a role in the pathogenesis of rheumatic fever.

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ABSTRACTS

DIFFERENTIAL SHEEP CELL AGGLUTINATION TEST FOR RHEUMATOID ARTHRITIS

S EDWARD SULKIN, ROBERT M. PIKE AND HOWARD C. COGGESHALL

Rose and his associates recently described a sheep cell agglutination test which may prove to be helpful as an aid in the differential diagnosis between rheumatoid arthritis and other diseases with arthritic manifestations It was shown that a sixteen-fold difference or greater between agglutination titers of normal and sensitized sheep erythrocytes occurred almost exclusively with sera from patients with rheumatoid arthritis

The differential sheep cell agglutination test of Rose and his associates was performed with serum specimens from forty-three persons with rheumatoid arthritis

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DISCUSSION*

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main agree with those reported by Drs Sulkin, Pike and Coggeshall. The differential titers found by us are best seen from the curves in Figure 118 Those per-

* By Dr Nanna Svartz.

been remarkably small We do not, therefore, consider that we are able to pass any definite judgment yet on the possible existence of a parallelism between the differential titer and the activity of the disease

As described in my discussion of Dr Boots' paper,* in the course of our work on [illegible] corpuscles, can as a rule be suppressed if the patient's serum has previously been absorbed with normal, i e., nonsensitized red blood corpuscles It is true that a slight agglutination may occasionally remain if the reaction is carried out with sensitized blood corpuscles This agglutination can usually be induced to disappear by renewed absorption with normal blood corpuscles

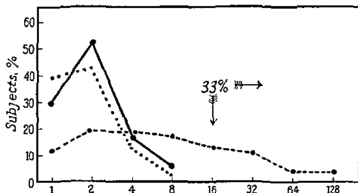


Fig 118 Differential agglutination titers of ninety rheumatoid arthritis patients (broken line), sixty-five patients with diseases other than rheumatoid arthritis (dotted line), and fifty-two presumably normal persons (solid line)

With rheumatoid arthritis, however, the case is quite different Here, only those agglutinins which give rise to agglutination with unsensitized blood corpuscles are absorbed by normal sheep cells, whereas the reaction carried out with sensitized sheep blood corpuscles remains unaffected To judge from the experiments we have so far carried out, this absorption reaction is constantly appearing in rheumatoid arthritis, if a special method is used

Certain bacteria give rise to antisheep cell agglutinins upon injection in, for example, rabbits, while others do not Enterococci in particular induce strong antisheep cell agglutinins We especially studied these bacteria because I have used them for many years in various attempts to induce experimental arthritis in animals.

By injecting enterococci into rabbits it is possible to induce a chronic articular infection which does not at first give rise to the rheumatoid arthritis reaction But after the disease has been going on for some months it may be possible to demonstrate the typical reaction We do not yet know how frequently this is the case

In the experiments so far carried out only enterococci and certain types of pneumococci (especially type 42) have given rise to antisheep cell agglutinins after injection into animals It is important to note that injections of beta hemolytic streptococci, Lancefield's group A, do not give rise to hemagglutinins, nor do staphylococci or *Salmonella typhosa*

* See p 342

SENSITIZATION WITH TISSUE ANTIGENS

PHILIP A CAVELTI

The literature on experimental sensitization with tissue antigens is reviewed, with emphasis on homologous tissue materials in conjunction with bacterial products In the author's own work immunization of animals with mixtures of homologous kidneys and killed group A beta hemolytic *streptococci led to the formation* of autoantibodies to kidney, as demonstrated in vitro, and, by in vivo reaction of these antibodies with the kidney, to acute and chronic glomerulonephritis Similar immunization of animals with homologous heart or connective tissue in mixture with killed streptococci initiated production of autoantibodies to cardiac or connective *tissue substances, also demonstrable in vitro with extracts of these tissues* As a result of the reaction of these antibodies with the tissues in situ, lesions of the rheumatic type developed, especially endocarditis and myocarditis, but also widespread lesions in the perivascular connective tissue

By means of the collodion particle technic, autoantibodies to human heart extracts have been demonstrated in the serum of patients with active rheumatic fever. Technical difficulties, especially as regards the activity of the tissue antigens, have led to the search for a method giving more consistent results Preliminary findings of complement fixation studies indicate the presence of antibodies to human tissue components in active rheumatic fever

DISCUSSION*

Clinical experience and epidemiologic studies strongly implicate the beta hemolytic streptococci in the causation of glomerulonephritis and rheumatic fever. At the same time, failure to demonstrate the organism in affected tissues, and the

of the organism and the pathologic changes produced The possibility that this interposed host reaction is a sensitization, particularly to body tissues combined with or altered by bacterial products, is in accord with many clinical features of

lative medicine without experimental evidence such as that produced by Dr Cavelti that such antibodies can be produced in animals and that pathologic changes analogous to those seen in the human diseases can be produced by these procedures

The difficulty in demonstrating such antibodies in patients with rheumatic fever may be, as the author suggests, due to technical factors There is also the possibility that such antibodies are not present in the circulating blood in detectable amounts, perhaps due to fixation in the tissues. In this connection it would be

* By Dr William D Robinson

tissue is more potent than other connective tissues In sera of patients with rheumatoid arthritis, no antibodies to human joint tissue antigen capable of producing antibodies in rabbits could be detected

This concept is not incompatible with other lines of investigation in rheumatic diseases The work of Fulton and Marcus, identifying certain hyaluronidase inhibitors with some components of complement, suggests at least a relationship of immunologic phenomena with the hyaluronic acid-hyaluronidase story More immediately pertinent is the reciprocal relationship between immunologic reactions

tissues analogous to those discussed in this paper It is therefore necessary in studies of this sort, where injections of antigens are continued over long periods of time, to determine whether the changes produced result from a specific immunologic reaction or are a manifestation of nonspecific stress operating through the pituitary-adrenocortical mechanism.

ANTIGENIC PROPERTIES OF HYALURONIDASE INTRODUCED INTO THE STUDY OF RHEUMATIC DISEASES

CATHARINE E LOGAN

Intradermal injections of 1 1000 hyaluronidase (0 15 turbidity reducing unit per cc) with 1 per cent methylene blue were given to eighty-one persons to determine the incidence of skin sensitivity in patients with arthritis and in controls The results were positive in fifty-nine of sixty-two patients with atrophic arthritis, in one of three patients with hypertrophic arthritis, and in seven out of eight patients with mixed types Only one of the controls showed a slightly positive test

In a number of the patients exhibiting positive tests, a cutaneous nodule developed which lasted from three to fourteen days. Round cell infiltration, small areas of necrosis and occasional giant cells were seen in the several instances in which a biopsy was performed

Several patients with atrophic arthritis were given a series of injections of small amounts of hyaluronidase in an attempt at desensitization The results were inconsistent although improvement was noted in a few instances

It is concluded that sensitivity to hyaluronidase may play a part in the development of arthritic changes, in view of the tissue response at the site of injection The possibility is also considered that desensitization may alter the course of the disease

STUDIES ON BLOOD PLASMA AND AMINO ACIDS

ELECTROPHORETIC ANALYSIS OF THE PLASMA PROTEINS IN RHEUMATIC DISEASES, ESPECIALLY RHEUMATOID ARTHRITIS

BORJE OLHAGEN

For many years it has been agreed that the increased sedimentation rate in arthritis is a reliable criterion of activity, but not until lately have we realized the complexity of changes in the plasma protein pattern that alter the suspension stability of the blood The sedimentation rate is dependent primarily on the fibrinogen concentration, but the globulins and even the albumins also seem to have influence However, the plasma globulins and albumins are not accessible to an exact chemical determination With ordinary salt fractionation methods only the grosser alterations are detected, so the finding of a normal albumin/globulin quotient need not signify the absence of globulin changes Now the electrophoretic separation method as developed by Tiselius has greatly increased the possibilities of differentiating the plasma proteins, especially the globulins During the last seven years we have examined about 180 cases of arthritis and allied conditions electrophoretically[1] As we have used different buffers, only a part of the material that is homogeneous with respect to the buffer composition will be presented

CLINICAL STUDY

Rheumatic Fever The cases of rheumatic fever have been divided in two parts (Table 57) One group, called "simple acute polyarthritis," represents cases with localized symptoms, mainly in the joints, the other, called "complicated acute polyarthritis," comprises cases with additional involvement of the heart or rheumatic manifestations from other organs In this group relapsing cases of rheumatic fever are also included The blood examination was carried out when the disease was estimated to have reached its maximum with respect to the sedimentation rate Common to all cases is a reduction of the albumin, a pronounced alpha globulin increase (with few exceptions) and a fibrinogen increase throughout, the beta component being within the normal range As regards the gamma globulin the two groups differ With few exceptions the simple cases show hardly any increase of this component, whereas the complicated cases display an obvious increase in the gamma globulin With beginning regression of the disease the alpha globulin and the fibrinogen first return to normal values and ultimately the gamma globulin also returns When the sedimentation rate has returned to normal there are no longer any significant alterations in the electrophoretic pattern

Rheumatoid Arthritis As will be seen from Table 57 there is also a divi-

sion of the cases of rheumatoid arthritis. One group represents only typical rheumatoid arthritis or the syndrome we in Scandinavia often call "primary chronic polyarthritis." The other group consists of chronic arthritis secondary to focus of infection[2] including atypical cases of rheumatoid arthritis. The general changes are hypoalbuminemia, moderately raised values of alpha globulin and a moderate increase in fibrinogen and gamma globulin. The cases of true rheumatoid arthritis show much more elevated gamma globulin values than the cases of secondary chronic arthritis. As to the clinical course there are also differences. the primary cases are severe or moderately severe, with a long history (at least one year), whereas the secondary cases are generally characterized by shorter duration and frequent occurrence of remissions. The average values might give a false impression of uniformity. Among the primary cases there are five severe cases exhibiting gamma globulin values within the normal range. It is of interest that all of

*Table 57 Relative Plasma Protein Concentrations in Acute and Chronic Forms of Articular Rheumatism**

DESCRIPTION AND NUMBER OF CASES	ALBUMIN,	α	β	φ	γ	TOTAL PROTEIN
	%	%	%	%	%	%
Normal values (10)	56.2	7.0	14.0	4.0	18.8	7.7
Range ($\pm 2\sigma$)	50.8–61.6	4.8–9.2	9.8–18.2	3.0–5.0	15.4–22.2	
Rheumatic fever						
Simple acute polyarthritis (19)	43.6	12.1	14.4	9.6	20.3	7.6
Complicated acute polyarthritis (8)	37.6	12.3	13.8	7.8	28.5	7.8
All cases (27)	42.0	12.2	14.2	8.8	22.8	7.7
Rheumatoid arthritis						
Primary chronic polyarthritis (40)	41.7	9.2	14.2	7.3	27.6	7.7
Secondary chronic polyarthritis (26)	42.9	10.6	15.6	8.5	22.4	7.5
All cases (66)	*42.0*	*9.7*	*14.8*	*8.0*	*25.5*	*7.6*

* Buffer composition: 0.032 molar sodium phosphate, 0.004 molar sodium biphosphate, and 0.15 molar sodium chloride, *p*H 7.6

these patients had been treated with gold before the last exacerbation. It might be coincidental, otherwise it would indicate that gold interferes with gamma globulin production. In fact, two of the five cases also had signs of injury to the hematopoietic apparatus in the form of thrombocytopenia. It should be emphasized, however, that the protein changes in rheumatoid arthritis occurred in hospitalized cases with fully developed arthritic symptoms. In the very early beginning of the disease the electrophoretic pattern may be without significant changes and the sedimentation rate may be low. The first sign seems to be an increase in alpha globulin.[3] About half of the cases of secondary chronic arthritis show rather low gamma globulin values, the other half elevated values. Generally these latter represent the more severe cases, both with respect to the extent of the tissue changes and the duration of the disease.

COMMENT

How should we interpret these varying protein changes in articular rheumatism? From an electrophoretic point of view they are altogether nonspecific. Generally the tissue response to different kinds of stress is reflected in the plasma protein pattern and we may distinguish two main phases, one acute defensive and one chronic reparative reaction, often in combination. The former occurs in febrile and exudative conditions such as acute infections, and in processes with tissue destruction such as burns, contusions, infarctions, and malignant tumors. The electrophoretic characteristics in this phase are increases in alpha globulin and fibrinogen. The acute phase- or C-reactive-protein forms only a small part of this alpha globulin increase. The nonspecific chronic reparative reaction is principally characterized by gamma globulin increase and hypoalbuminemia, and most often by a fibrinogen increase. Actual conditions of this type are, for example, later stages of acute infections, chronic infections of various types, parenchymatous disorders of the liver, especially cirrhosis, disseminated lupus erythematosus, and periarteritis nodosa. Part of the gamma globulin increase is actually specific, at least in an immunologic sense, i.e., it is due to antibodies. It should be emphasized, however, that the antibody response to the recognized antigens in arthritic conditions forms only a small part of the bulk of the gamma globulin.

I have carried out absorption experiments which show that removal of the agglutinins against streptococci or enterococci in rheumatoid arthritis does not palpably alter the electrophoretic pattern of serum, and Dole[8] has found the same with antistreptolysin in rheumatic fever. There is no apparent correlation between the gamma globulin concentration of plasma and the titer of streptococcal agglutinins, either the antistreptolysin or the differential agglutination of sheep red cells. This absence of explanation for the gamma globulin increase in rheumatoid arthritis and rheumatic fever may indicate either that we still have not found the actual antigen or that the phenomenon is essentially nonspecific. I might point out the principal electrophoretic similarity between severe forms of rheumatoid arthritis and disseminated lupus erythematosus, both diseases affecting the connective tissue and both with a high gamma globulin content. Perhaps degradation products from the affected mesenchymal tissues do stimulate the formation of autoantibodies.

One may ask if the electrophoretic analysis will be of any help in judging the individual case of arthritis. We have seen that the same changes may occur in both rheumatic fever and rheumatoid arthritis, for example, the common type of pattern with both alpha and gamma globulin increase, where it is not possible to differentiate the two conditions by means of electrophoresis. But the electrophoretic analysis provides a conception of the actual phase of reaction that affords a better understanding of the situation. For instance, in an acute case with a joint exudate the finding of high alpha globulin and fibrinogen values together with a normal gamma globulin concentration argues for a simple exudative reaction with probably rapid restitution. On the other hand, a pronounced increase in gamma globulin is suspicious for a more deep-seated lesion and accordingly a more protracted course of the disease. Hence the electrophoretic analysis in some of the untreated cases may give diagnostic and prognostic guidance.

this connection it should be mentioned that uncomplicated cases of osteoarthritis display normal electrophoretic patterns.

In arthritis of various types the plasma proteins often appear as components of another body fluid, the joint exudate. Electrophoretically the normal synovial fluid contains four visible components: albumin, beta globulin, gamma globulin and hyaluronic acid.[8] This latter is, however, not accessible to quantitative electrophoretic analysis. The acute exudate in rheumatic fever shows a pattern which corresponds strikingly to the plasma

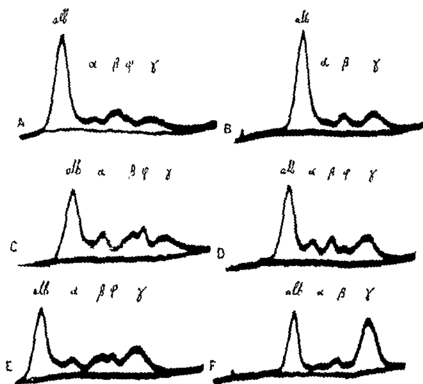


Fig 119. Electrophoretic diagrams: A, normal plasma; B, synovial fluid from a patient with traumatic synovitis; C, plasma, and D, acute exudate from a patient with rheumatic fever; E, plasma, and F, chronic exudate from a patient with rheumatoid arthritis.

diagram. All the protein components are represented and the total protein

expected since these proteins have the largest molecules The joint fluid in traumatic synovitis generally shows a low total protein value but the relative concentrations of the components are of approximately the same order as those of the corresponding plasma; the fibrinogen component, however, is often missing in cases of long-standing hydrops. The chronic

is produced locally The more probable explanation, however, is that molecules of different size may have different reabsorption rates through the pathologically changed synovial membrane or tissue The intra-articular hydrostatic pressure is presumably also a factor of varying importance. Although the pathogenesis of these changes is still obscure, there remains the differential diagnostic value of the electrophoretic analysis as a part of the synovial fluid examination [3]

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ONE YEAR'S EXPERIENCE WITH POSTPARTUM PLASMA IN RHEUMATOID ARTHRITIS*

LOUIS W. GRANIRER AND A W VICTOR

In a previous report,[1] encouraging observations were noted in the use of postpartum plasma infusions in a case of psoriatic arthritis On the basis of this paper and in confirmation of previous studies,[2] it seemed worthy of a clinical trial to determine the therapeutic possibilities of postpartum plasma in rheumatoid arthritis This report is concerned with the results observed in patients with rheumatoid arthritis who received postpartum plasma infusions at the Queens General Hospital Arthritis Clinic during the twelve-month period March 5, 1948, to February 28, 1949.

MATERIALS AND METHODS

Eight patients with active and moderately advanced rheumatoid arthritis were studied In this group there were two men and six women, their ages varied from thirty-eight to sixty-three, and the duration of the arthritis ranged from two to ten years Each patient fulfilled the criteria for rheumatoid arthritis as established by the American Rheumatism Association,[3] and had been refractory to all previous therapy No advice was given as to special diets, medication, bed rest, vitamins or physiotherapy Appropriate clinical, hematologic and roentgenologic examinations and weight recordings were made at regular intervals

Once a week, for three to six months, 250 cc of pooled postpartum plasma was administered intravenously to each patient The dose was reduced as the clinical condition warranted

As a control, six similar patients were studied for the purpose of evalu-

* From the Arthritis Clinic of the Queens General Hospital, Jamaica, New York. The authors express appreciation for the liberality and interest of the Medical Board of the Queens General Hospital in supporting this study, and acknowledge the coop[eration of the] Obstetrical Department, the Blood Bank and the Laboratory

ating the effect of normal plasma on rheumatoid arthritis. Each patient received weekly infusions of 250 cc of normal plasma and the clinical and laboratory course was observed.

OBSERVATIONS IN THE POSTPARTUM GROUP

In general, the characteristic response in the group injected with the

The involved knee joints usually *were the first to improve In two patients* the subcutaneous nodules on the forearm gradually disappeared. Six cases that had previously been refractory or intolerant to gold salts therapy responded dramatically to the postpartum plasma. All of the patients gained weight· The vasomotor and trophic disturbances of the extremities reacted favorably with the clinical progress and the hypochromic, microcytic anemia showed a slow, steady improvement In most of the patients the albumin/globulin ratio was restored to normal The sedimentation rate remained *unaltered except for two cases Total leukocyte counts* exhibited *no abnor*malities other than a tendency toward leukopenia. The Aschheim-Zondek tests were negative in all the treated cases.

In 320 transfusions with postpartum plasma there were no cases of homologous serum hepatitis nor any febrile reactions Two patients had a mild urticaria which was relieved with antihistamine therapy. Transient reactions such as flushing, fullness in the head, and tingling of the lips were not uncommon, but in each case the symptoms passed off a few minutes after the end of the infusion

According to the criteria for grading therapeutic results established by the New York Rheumatism Association,[4] the group treated with postpartum plasma could be classified as a grade II, or major improvement. This group did not show systemic signs of rheumatoid activity, such as leukocytosis and fever Joint inflammation, as characterized by heat and redness, subsided and joint swellings were minimal No new rheumatoid process of intra-articular or extra-articular nature developed and the remaining impairment of joint function due to muscular *spasm was slight or absent. Although the* erythrocyte sedimentation rate was usually elevated it was less than 50 mm per hour (Westergren)

From our observations it appears that the ideal procedure would be to administer this plasma for months, and that the clinical response is more *rapid* with the larger amounts of postpartum plasma infusions The remissions were sustained in an average of three to twelve weeks after cessation of therapy

RESULTS WITH NORMAL PLASMA IN CONTROL GROUP

Continuation of treatment for eight to twelve weeks in the control series with normal plasma led to a surprising failure Of the *six patients under* observation, five either failed to improve or actually felt worse The sixth patient thought he was slightly better In this group there was no spontaneous sense of well-being and no evidence subjectively or objectively of any benefit in the course of the arthritis The laboratory results were unaltered

COMMENT

It has been observed that pregnancy may initiate a beneficial effect u the course of rheumatoid arthritis In the present investigation of patie treated with postpartum plasma a definite effect on the joint lesions w noted The course of rheumatoid arthritis is variable and there is no metho of predicting the degree of resistance of an individual patient Rapid anc extensive resolution, even of large and well established joint lesions, occasionally occurs on a regimen of good nursing care, bed rest and orthopedic measures Thus it is debatable that the administration of a specific agent could be the cause of the amelioration of the arthritis In the eight patients with rheumatoid arthritis in the present study, the institution of postpartum plasma was followed in every instance by a measurable degree of clinical and laboratory improvement In these patients there was a marked improvement in their sense of well-being, joint swelling and tenderness subsided, and joint motion was considerably restored It would seem logical to assume, therefore, that the beneficial results noted in this series of eight patients were attributable to the postpartum plasma

The course of the rheumatoid arthritis in the six control cases treated with normal plasma infusions was in striking contrast to that observed in the postpartum plasma series One patient was definitely worse and refused further treatment, and the others showed unsuccessful results

From our observations and from roentgenologic studies, it appears likely that the arthritic lesions are reversible to a considerable degree

Rheumatoid arthritis involving both knees usually represents a stubborn complication Natural healing may occur but it is slow and uncertain The rapid disappearance of the synovitis in these areas was observed almost uniformly after the administration of postpartum plasma

The principal effect of the treatment was to produce a remission where gold salts had previously failed

THEORIES AS TO THE PROBABLE MODE OF ACTION OF POSTPARTUM PLASMA

Fortunately pregnancy confers an increased degree of resistance to a number of infectious diseases This protection often extends throughout the entire period of pregnancy and for several weeks after parturition Repeated observations have confirmed the favorable effect of pregnancy on the course of rheumatoid arthritis Apparently scarlet fever rarely occurs in pregnancy, only twenty cases are recorded in the literature [5] Hudson, Cook and Adair[6] noted that forty-six of forty-eight sera derived from women in various stages of pregnancy neutralized the herpes virus in vitro

Because of the profound changes in the general activity of the endocrine glands, it is not surprising that alterations in the mechanisms of resistance do occur During pregnancy, the glomerular zone of the suprarenal glands becomes hypertrophied and stores lipids in great quantity [7] It is possible that this increase in lipids may be significant in raising the resistance of the individual to certain types of acute infections Hypertrophy and increased function of the anterior lobe of the pituitary gland produces a greater activity of the adrenotrophic as well as the spleen-stimulating factors There is an increase in the progesterone and gonadotrophic hormones What part the increased activity of the thyroid gland and the persistence of the corpus

luteum plays in the defense mechanism during pregnancy is at present undetermined. Less is known as to the hormones secreted by the fetal glands.

In the early phase of pregnancy the excretion of estrogens rises slowly from normal values found in the menstruating woman, so that at about the eighth week there are from 2,000 to 10,000 international units of total estrogens.[8, 9] The values then increase gradually to from 15,000 to 40,000 or even more international units at term Immediately before delivery, estrogens decrease precipitously to very low levels. These estrogens are in both the free and combined forms, predominantly the latter, which can be tested biologically only after hydrolysis to the free or active form Pregnanediol excretion is at a relatively low value up to about the third month, ranging from 5 to 25 mg. daily. There is a rather steep rise in daily excretion to about 100 to 150 mg. during the last few months of gestation, and a steep drop a few days before term to low values approaching those of the normal luteal phase (4 to 15 mg.) Chorionic gonadotrophin excretion differs in pattern from the foregoing two substances. The hormone appears fairly promptly in the urine in increased quantities, so that it can be detected two weeks after the missed period by the injection of urine into rabbits (Friedman test). These values range between 1,000 and 5,000 rat units daily By the thirtieth day, however, there is a definite explosion in excretion, approaching 100,000 rat units in twenty-four hours, and on about the fortieth to the sixtieth day there may be even a higher concentration up to 800,000 rat units daily Following this sharp peak in excretion there is a [illegible] 000 to 10,000 rat units daily [illegible] ble amount occurs. [illegible] d pregnenolones increases gradually and rather rapidly during the last two-thirds of gestation while that of 17-ketosteroids shows only a very slight rise The ordinary elimination of the gonadotrophin reaches a maximum toward the end of the second month and falls to low levels when the excretion rates for the first mentioned four products begin to rise sharply. The corticoid elimination in the urine shows a double peaked curve, with one maximum coincident with the peak of the gonadotrophin excretion and the second maximum between the two hundredth and two hundred and fortieth day of gestation. Noteworthy quantities of corticoid activity can be extracted from the corpus luteum, presumably because progesterone possesses corticoid potency. Folliculoids elicit a pronounced and specific type of cortical hypertrophy According to Marrian's theory[9] of C-17 side-chain oxidation, corticoids could be formed from progesterone by oxidation between C-17 and C-17[1]

Other profound chemical changes occur during pregnancy which may well influence the constitutional response In the literature are certain references which are in harmony as to the influence of pregnancy upon the lipids of the blood "Thus in 1904 Capaldi . . . noted that the blood fat of dogs late in pregnancy was almost double that of the nonpregnant animal This is quoted by Bar, in 1907, who adds his own observation that the serum of pregnant women appears white and, as there is an abundance of fat in the viscera at this time, he is not surprised to find it increased in the blood."[10] One of the most important changes in pregnancy is this marked

increase in the plasma neutral fat during the first trimester and in cholestero and phospholipids during the second trimester. At term the neutral fat i increased more than 100 per cent over that in the nonpregnant women i The lipemia of patients with active rheumatoid arthritis while pregnant is similar to that of normal pregnant women. Such changes may exert a favorable influence on the defense mechanism and may enhance antibody formation It is plausible that certain viruses could be inactivated by changes in the surface tension through alterations in the serum lipids [12] For example, the virucidal titer to the poliomyelitis virus of the sera of pregnant women is considerably higher than that of normal women [13] Kuzell and Davison[14] demonstrated that the average serum lysolecithin values as measured by the amount of hemolysis of standard human erythrocytes were found not to vary appreciably in rheumatoid arthritis, pregnancy, jaundice, and in normal persons as controls

Specific alterations in the protein content of pregnant sera were noted by Moore and his associates [15] They showed that as the albumin of the maternal sera decreases during pregnancy, the alpha and beta globulins, particularly beta globulin, increase greatly The gamma globulin remains essentially unchanged and at delivery the albumin/globulin ratio remains 1 It was observed by Pedersen[16] that in human sera it is the beta globulin that contains the large lipoprotein complexes

As mentioned originally by Still[17] in 1897 and confirmed and elaborated later by Hench[18] in 1938, jaundice--not the hemolytic but the hepatic type --may produce a remission in rheumatoid arthritis Subsequently it was shown that in hepatic jaundice, as well as in pregnancy, the serum contains a large amount of beta globulin along with a high content of cholesterol On the other hand, hemolytic jaundice even though quite severe did not produce this significant alteration in the electrophoretic pattern of the serum [19] It is our theory that this beta globulin distortion described in hepatitis and pregnancy may be the specific ameliorating factor in rheumatoid arthritis [20]

It is interesting to note that the electrophoretic fractions designated as albumin, alpha, beta and gamma globulin do not consist solely of protein but represent native complexes of these proteins with low molecular weight, nonprotein substances Thus according to Tiselius[21] the albumin fraction contains bilirubin in addition to carbohydrate, while the beta globulin contains an appreciable amount of the lipids such as cholesterol It was subsequently demonstrated that all serum protein fractions obtained by electrophoretic separation contain some cholesterol and phosphatides in bound form although the alpha and beta globulins are richer in lipids than either albumin or gamma globulins, likewise all fractions were found to contain carbohydrate, with the alpha and beta globulins again showing the highest percentage [22]

Even incorrect theories are often of great help in unveiling the secrets of nature. In the rheumatoid process, it is possible that there is a defect in the defense mechanism as well as a state of relative multiglandular imbalance It is plausible that postpartum plasma not only provides immune bodies and enzymes but helps to restore the anterior lobe of the pituitary to its central position in the endocrine system as chief coordinator of the various endocrines and their hormone requirements

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STUDIES OF THE URINARY EXCRETION OF AMINO ACIDS IN PATIENTS WITH RHEUMATOID ARTHRITIS

A Preliminary Report

CHARLES A. L. STEPHENS, JR., ALICE BORDEN, W. PAUL HOLBROOK, DONALD F. HILL, LEO J KENT, EVELYN B. WALLRAFF AND A. R. KEMMERER

The etiology of rheumatoid arthritis is unknown Because of the well known antirheumatic effects of pregnancy, jaundice, transfusion, and gold, it has long been the belief of the authors of this paper that the common denominator responsible in these instances for remission of the disease is of a metabolic nature

The reported alterations in amino acid excretion and/or blood concentration in pregnancy and jaundice [1, 2] suggested that rheumatoid arthritis may be directly or indirectly associated with intrinsic metabolic disturbance of protein metabolism The weight loss and many of the systemic

manifestations which are common to both protein imbalance and to rheumatoid arthritis lend credence to this hypothesis

Further, changes in the utilization of specific amino acids have been shown to result in characteristic symptomatology in both animals[3,4] and in human beings[2,5,6,7,8] It therefore seemed valid to institute investigations of amino acid metabolism in rheumatoid arthritis This preliminary report concerns quantitative determinations of the urinary excretion of amino acids in rheumatoid arthritis

METHODS

Selection of Patients One hundred twenty-seven patients were selected for study There were fifty-four males and seventy-three females All had varying degrees of activity of indisputable rheumatoid arthritis of the following types Ten spondylitis cases, 106 peripheral rheumatoid arthritis cases, and eleven cases of spondylitis and peripheral rheumatoid arthritis combined. There were two patients with peripheral rheumatoid arthritis who underwent pregnancy remission The ages ranged from 16 to 72 with a mean average of 43 4 None had had gold injections within a year or transfusions within a month prior to the specimen collection Controls were persons who apparently were in good health There were fifty-three males and seventy-one females Certain of the amino acids were assayed in 24-hour urine specimens from seventeen normal pregnant women

Collection and Treatment of the Urine Specimens All 24-hour urine specimens were collected under toluene in the usual manner, and sampled within two hours of the last voiding All specimens, including free and hydrolyzed samples, were set up within twelve hours of collection of the specimens Concomitant food intake was recorded Urine volumes were measured and recorded and all were diluted to 2000 cc before sampling If the volume was above 2000 cc no dilution was made

Methods of Assay 1 For determination of free amino acids, 10 cc of urine was neutralized to pH 6 9 to 7 0 with sodium hydroxide or hydrochloric acid The neutralized urine was then transferred quantitatively to a 50-cc volumetric graduate and diluted to 50 cc This or another dilution made from this was used for assay Dilutions ranged from 1 5 to 1 100

2. For all determinations of total amino acids other than tyrosine and tryptophane, urine was autoclaved with hydrochloric acid as follows 10 cc of urine was pipetted into a 50-cc beaker and 1 5 cc of concentrated hydrochloric acid and 0 5 cc of water were added The samples were then autoclaved at 250° F for five hours After cooling, the pH was adjusted with concentrated sodium hydroxide to an end point between 6 9 and 7 0 The neutralized hydrolyzed urine was then quantitatively transferred to 50-cc volumetric graduates, diluted to 50 cc and filtered The filtrate (1 5 dilution of original urine was then appropriately diluted for assay

3 For total tyrosine determinations, sulfuric acid of the same normality was used instead of hydrochloric acid and the autoclaving was for one hour instead of five hours For total tryptophane determinations, the urines were subjected to alkaline hydrolysis

4 All samples were assayed in duplicate at four levels of concentration A standard curve for each amino acid assayed was determined with each series of specimens assayed, in each case from quadruplicate or triplicate samples of solutions of pure amino acids (Merck & Co or Baltimore Bio-

logicals) at seven levels of concentration. When the (*l*) form was unavailable, a double quantity of the (*dl*) form was used

5. Organisms used were *Leuconostoc mesenteroides* P-60, *Lactobacillus arabinosus*, and *Streptococcus fecalis* R. Assay media, storage media for stock cultures, and media for growing the seeding cultures were those of

Table 58 Amino Acid Assays of 24-Hour Urine Specimens in Rheumatoid Subjects

AMINO ACIDS	PATIENTS		AMINO ACID CONCENTRATIONS (All values in mg /24 hours) Free	Bound	Total	t VALUES* Free	Bound	Total
Tyrosine	Arth	17	15 9 ±10 3	26 4 ±12 2	42 5 ±17 6	0 86	3 65	2 06
	Norm	20	18 6 ± 8 4	14 6 ± 5 7	33 1 ± 7 3	2 08	2 46	2 99
	Preg norm	17	27 0	21 6	48 6			
	Preg Arth	3	33 0	18 2	51 2			
Valine	Arth	12	6 6 ± 4 0	13 1 ±10 4	19 1 ±11 6	0 7	0 7	0 2
	Norm	17	7 7 ± 4 2	10 7 ± 8 1	18 2 ±10 2			
	Preg norm	2	10 4	28 0	38 4			
	Preg. Arth	3	10 6	20 1	30 7			
Aspartic acid	Arth	13	3 8 ± 3 2	94 5 ±33 8	98 3 ±33 3	1 3	0 65	0 75
	Norm	14	2 4 ± 2 2	104 7 ±36 9	107 1 ±37 0			
	Preg norm	1	4 3	121 7	126 0			
	Preg Arth	1	7 5	122 7	130 2			
Arginine	Arth	14	7 2 ± 1 1	32 1 ±17 7	39 3 ±17 8	1 18	0 8	1 06
	Norm	15	5 6 ± 1 3	27 7 ±11 4	33 2 ±12 6			
	Preg norm	1	11 2	34 4	45 6			
	Preg Arth	1	13 9	41 5	55 4			
Histidine	*Female*							
	Arth	15	68 1 ±42 3			1 66		
	Norm	13	99 4 ±55 5			6 16		
	Preg norm	17	*429 0*					
	Preg Arth		609 0					
	Male							
	Arth	10	155 5 ±53 7			1 62		
	Norm	12	198 3 ±69 9					

* t value is a factor indicating statistical significance

Snell and Henderson [9] For glutamic acid assays, the modifications suggested by Brickson et al [10] were followed For serine assays, a modification of the medium III of Sauberlich and Baumann[11] was used

6. Titration of lactic acid was performed with a potentiometer. Free and total amino acids for each sample were calculated from the same standard curve. Bound values were obtained by subtracting the free value from the total.

RESULTS

The patients studied suffered from varying degrees of activity of their disease, which may interfere with the exact interpretation of the reported results. Also, there are groups in this study which are composed of an in- . . . When

arthritis No controls using patients suffering from other diseases were studied No attempt was made to correlate age, sex, or duration of the disease with the results except as indicated for sex

Diet analysis for caloric protein intake indicates no significant differences between the patients and the controls This is not to be interpreted to mean that protein intake has no effect on amino acid excretion, but merely that our differences cannot be explained on the basis of a lower or higher protein intake. This is in accord with numerous other investigations [12, 13, 14, 15]

To date 1148 microbiological assays have been performed It will be noted (Table 58) that bound tyrosine occurs in the urine of patients with rheumatoid arthritis in significantly increased amounts The inadequate number of specimens from patients with rheumatoid arthritis in remission due to pregnancy does not permit interpretation, but the results are reported as obtained. Free tyrosine, free and bound valine, free and bound aspartic acid and free and bound arginine reveal no significant differences Free histidine in the urine of patients with rheumatoid arthritis is suggestively lower in concentration than in the urine of normal controls, although the wide variation in individual values does not validate this conclusion Further studies are being made

The state of pregnancy, both in controls and in the pregnancy remission state of rheumatoid arthritis, leads to a sevenfold increase in free histidine elimination This is in accord with previous investigations [1, 16, 17] The increased excretion of free tyrosine in pregnancy is in agreement with previously reported work [2]

Further studies are being made on urinary amino acids in active disease and in remissions due to pregnancy, jaundice, gold, transfusions, pregnancy transfusions and cortisone Blood concentrations are also under investigation and as these additional values are obtained in adequate series, they will be duly reported

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ABSTRACTS

ELECTROPHORETIC STUDY OF SERUM AND PLASMA IN RHEUMATOID ARTHRITIS COMPARISON OF RESULTS WITH THE FLOCCULATION AND OTHER TESTS

R ARMAS-CRUZ, M. MADRID, F. VALENZUELA, G LOBO-PARGA, C J. MEREDITH AND L COSTIN

The percentages of the several protein fractions, and the molecular mobility, were determined by electrophoretic methods in twenty-seven samples of serum and twenty-seven samples of plasma from thirty patients suffering from active rheumatoid arthritis In the serum of each patient the total protein and the albumin and globulin fractions were estimated by chemical methods and expressed in grams Flocculation tests (cephalin cholesterol, colloidal gold, colloidal red and thymol *turbidity) were also carried out, and the erythrocyte* sedimentation rate was determined by Westergren's method

T [illegible] the [illegible] were compared with the [illegible] higher than normal

The average molecular mobility for gamma globulin was significantly reduced in the rheumatoid group.

The albumin/globulin ratio determined by electrophoretic methods was roughly one-fifth lower than its chemical counterpart

The flocculation tests of the serum were also found to be positive in the majority of cases of active rheumatoid arthritis No constant relationship was apparent between this positivity and the quantitative changes in the protein fractions separated by electrophoresis

The erythrocyte sedimentation rate in rheumatoid arthritis correlated fairly closely with the relative quantity of fibrinogen.

Patients in this series were graded according to the relative severity of their disease processes Possible relationships existing between the clinical status and the electrophoretic findings did not appear to be significant. Electrophoretic analysis seems to be devoid of prognostic value in rheumatoid arthritis

TREATMENT OF RHEUMATIC DISEASES BY AMINO ACIDS

ALDO MASTURZO

Extensive studies, including estimations of the amino acid content of blood and synovial fluid, were performed in control animals and in animals suffering [illegible] h the blood amino [illegible] red in the synovial [illegible]

[illegible] of an amino acid compound containing molybdenum, seemed to induce chemical, histologic and [illegible]

[illegible] ults in 68 per cent of the cases of [illegible] an additional 22 5 per cent amelio- [illegible] d for those patients suffering from

peripheral rheumatoid arthritis (only 4 per cent failures), and osteoarthritis (1 per cent failures)

CONTINUED INVESTIGATIONS INTO THE PERIPHERAL CIRCULATORY AND METABOLIC PHENOMENA

EJNAR JARLOV

Interest in the reactions of the peripheral vessels to various physical agents has been increasing constantly and the demand for examination of these phenomena has become stronger Methods to determine these reactions were developed during World War II owing to the great importance of the peripheral circulation in aviation medicine Hertzman and his collaborators in St Louis have impro[illegible] nic by including reflecting light for electrophotomet[illegible] comes possible to examine reg[illegible]

Since 1943 the auth[illegible] eral pulse registration: [illegible] electrophotometric met[illegible] with penetrating light but now modified after Dr Hertzman's principle On the basis of this modification, a method was developed to measure the oxygen absorption in the skin, the technic may possibly be further modified into a quick method of measuring the standard metabolism of the organism

Combining these methods, investigations of the peripheral circulation and metabolism in normal people and in a number of diseases, especially poliomyelitis and rheumatic diseases, have been started

STUDIES OF CONNECTIVE TISSUE

THE HISTOPHYSIOLOGY OF THE CONNECTIVE TISSUES

SYLVIA H. BENSLEY AND ARTHUR W. HAM

All four of the primary tissues of the body exhibit structural specialization for the performance of special functions epithelial tissue for protection, secretion and absorption, muscular tissue for contraction, nervous tissue for irritability and conductivity, and connective tissue for support, nutrition and defense. The fact that a single tissue must support the other tissues of the body and at the same time nourish them and, if need be, defend them against aggression from infectious organisms, makes its histophysiology somewhat complex

THE SUPPORTING FUNCTION OF CONNECTIVE TISSUE

The human body is commonly described as a great community of cells It is more accurate to describe it as an edifice of intercellular substance in which cells live as residents Cells are jellylike, hence the form of the body is due largely to its content of these stronger and nonliving materials that are disposed between cells The intercellular substances—the building materials produced by the community of cells—are mostly confined to the connective tissue of the body, indeed, their manufacture and maintenance is one of the chief functions of the cells of connective tissue

There are several different kinds of intercellular substance found in connective tissue In our present state of knowledge it is convenient to classify these on morphologic grounds into two main types, the formed or fibrous type, and the amorphous type In most connective tissue these two main kinds are intimately mixed

There are three kinds of fibrous intercellular substances or fibers, collagenic, reticular, and elastic The first of these, the collagenic (or white) fibers, are the largest and most abundant With the light microscope collagenic fibers are seen to be composed of bundles of parallel fibrils Each of these is enveloped in a homogeneous material which binds the adjacent fibrils together in a fiber Collagenic fibers may be cemented together to form bundles, the fibers and bundles provide great tensile strength

Reticular fibers, on the other hand, are very delicate and are commonly disposed in the form of networks to provide intimate support for cells There has been some question as to whether they differ chemically from collagenic fibers A common opinion is that they differ only in size and that they are to be regarded as single free collagenic fibrils or very small bundles of them.

The third type of fiber is the elastic or yellow fiber Elastic fibers are less numerous and bulky than collagenic fibers and are widely distributed They appear as long, curving, branching fibers of a homogeneous highly refractile material, and as their name suggests, they contribute elasticity to the connective tissue

It is convenient to subdivide amorphous intercellular substances into ground substances and cement substances Ground substance is a term used

for sols or soft gels and cement substance refers to the more concentrated and rigid gels

The proportions of the various types of intercellular substance in the different connective tissues of the body vary *in relation to the particular* supporting functions of these tissues Where connective tissue need provide support only for cells, the intercellular substances consist chiefly of mixtures of reticular fibers and ground substance. Where connective tissue

strength, and elastic fibers the elasticity Ground substances in these tissues, with clefts for tissue fluid, contribute to their flexibility. In tendons and ligaments, where great tensile strength is required, collagenic fibers and cement substance constitute the bulk of the intercellular substance. For the *weight-bearing connective tissues, such as cartilage and bone, the fibrous* intercellular substances that contribute strength and a certain degree of elasticity to these tissues are solidified by the presence of a considerable amount of the cementing type of amorphous substance. This complex of fibers and cementing substance, moreover, provides a medium suitable for impregnation with calcium salts for still greater rigidity.

THE NUTRITIVE ROLE OF CONNECTIVE TISSUE

The nutritive role of connective tissue is determined by the fact that the blood and lymphatic vessels of the body lie within it and are all confined to this tissue. Since most cells do not abut on capillaries they must *be nourished from the connective tissue that separates them from capillaries* On consideration, it is evident that there are three possible mechanisms for cell nutrition by way of the connective tissue. (*a*) circulation of tissue fluid through large clefts, combined with diffusion of nutrient materials through the intercellular substance, (*b*) *diffusion of nutrient materials* through the bound water of gelled intercellular substance, and (*c*) diffusion of nutrient materials through tissue fluid in minute clefts with minimal circulation of tissue fluid

Normally, tissue fluid with its nutrient crystalloids is produced as a dialysate of blood plasma through the living semipermeable membrane of endothelium at the arterial ends of capillaries. This is because the capillary hydrostatic pressure, though not great, is greater than the difference between the osmotic pressure of the colloids of the blood and that of the tissue colloids Some of the tissue fluid emerging from the arterial ends of capillaries, and after circulating through the tissue spaces, is returned at *the venous ends of capillaries* where the hydrostatic pressure has become

When any one of the factors *in this process is altered, excess tissue fluid* is produced For example, venous obstruction increases the venous hydrostatic pressure and this interferes with the resorption of tissue fluids into the capillaries Again, lowering of the osmotic pressure of the blood colloids by depletion of blood proteins causes edema, as does also *increased* permeability of capillary endothelium due to injury to it.

In areolar tissue which is flexible the tissue fluid formed as a dialysate

of blood plasma may circulate in the large tissue clefts In addition, diffusion of nutrient materials between capillaries and cells may occur through the ground substance

In the more rigid types of connective tissue, however, there are no large clefts for the circulation of tissue fluid In cartilage which is nonvascular, the cement substances provide a means whereby dissolved crystalloids may diffuse between capillaries and the cartilage cells. However, when cartilage cells mature and hypertrophy, they liberate alkaline phosphatase which results in the calcification of the intercellular matrix This in turn interferes with the diffusion of nutrient materials through the dispersion medium of the gel So, in calcified cartilage the cells must die Calcified cartilage therefore can hardly be a permanent tissue for rigid support

In bone, on the other hand, tiny clefts or canaliculi that contain tissue fluid permeate the intercellular substance Hence, bone cells may be nourished by the diffusion of the nutrient materials through tissue fluid in these tiny clefts though they reside in a calcified matrix Therefore, bone can persist as a living calcified weight-bearing tissue, this is the reason for bone having supplanted calcified cartilage for this purpose

THE DEFENSIVE ROLE OF CONNECTIVE TISSUE

In playing a defensive role, connective tissue serves as the "arena of inflammation" The vascular and specific cellular activities inherent in the inflammatory process are well known The intercellular substances by their character and composition may act, in addition, as a barrier to the spread of infection Certain depolymerizing enzymes such as hyaluronidase have been shown to increase the spread of certain infections by changing the character of the intercellular substance

RELATIONSHIP OF CELLS TO INTERCELLULAR SUBSTANCES

There is an intimate relationship between connective tissue cells and intercellular substances Changes in the one are reflected in the other Characteristically, the undifferentiated cells of mesenchyme are associated with an optically homogeneous intercellular substance that contains disperse (or scattered) proteins and polysaccharides in a sol-gel state Differentiated fibroblasts are associated with a more differentiated combination of fibrous proteins oriented and cemented into fibrils and fibers with the cement type of amorphous substance Osteochondrogenic cells are associated with similar constituents in slightly different proportions Moreover, osteochondrogenic cells can manufacture alkaline phosphatase, which is so important in the mechanism of calcification

AGING AND REPAIR PROCESSES

Most differentiated connective tissues contain a large proportion of differentiated cells, but they also have a small proportion of less differentiated cells with great developmental potentialities Thus in areolar tissue the majority of the cells are differentiated fibroblasts, macrophages, fat cells and mast cells The functions of the first three are clear, but the role of the mast cells is, as yet, obscure It has been suggested that they elaborate or store heparin and that this is contained in their distinctive granules The relation of heparin, a sulfated mucopolysaccharide, to the other mucopolysaccharides of the intercellular substances, and its function in the connective

tissue, are as yet unknown. Besides these differentiated cells there are less differentiated cells which may give rise, from time to time, to any of the others as the need arises.

So also in cartilage and bone most of the cells are well differentiated cartilage or bone cells But in the cellular layer of the perichondrium or periosteum reside less differentiated cells, which can give rise to fiber-forming cells, chondroblasts, osteoblasts, osteoclasts, or more of the undifferentiated cells.

In repair phenomena, as also in the process of aging, there is a shift from the less differentiated to the more differentiated types of cells and intercellular substance—an acceleration, as it were, of the maturation process. For example, in areolar tissue, as scar formation proceeds following an injury, more of the collagenic fibrous intercellular substance is formed with a diminution of the ground substance

THE CONNECTIVE TISSUES OF JOINTS

Joints develop as specialized areas of connective tissue In the dense core of cellular mesenchyme of a developing limb, areas of amorphous *intercellular substance appear as clefts in the regions where joints are to* develop. These clefts in the cellular mesenchyme are the definitive joint spaces but are actually filled with amorphous intercellular substance

In a movable or synovial joint four types of connective tissue exist in relation to a connective tissue space filled with amorphous intercellular substance. Hyaline cartilage provides the bloodless and nerveless articular surfaces. The synovial membrane and joint capsule are composed of areolar, adipose, and fibrous connective tissue Areolar tissue occurs where there is greatest movement and least tension Adipose tissue occurs between pressure areas, and fibrous tissue where greatest tensile strength is required, as in the strengthening tendons and ligaments. The synovial fluid acts as a *lubricant and source of nourishment for the articular cartilage cells.*

The synovial fluid is a sol in which tissue fluid may be thought of as the dispersion medium and the hyaluronic acid as the disperse phase. It is probable that the tissue fluid is derived from the blood capillaries of the synovial membrane The polysaccharide may be elaborated *by the less differentiated* cells of the areolar connective tissue directly into the joint space, or be washed there from the ground substance by the circulating tissue fluid

THE CHEMICAL COMPOSITION OF THE CONNECTIVE TISSUES*

KARL MEYER

The amorphous ground substances, rather than the formed elements, are now generally considered to be the primary sites of the pathologic processes which we combine under the name of rheumatic diseases Our knowledge of the chemical nature and physiologic reactions of the ground substances, and specifically of the interfibrillar matrix, is still scant, despite the fact that they have been described and studied histologically by many investigators There are reasons for this slow progress The quantity of the material is extremely small compared with the bulk of the formed elements, and the physiologic reactions and transformations of this material are apparently rather slow and therefore difficult to detect. In our laboratory we have attempted for many years to isolate and to characterize the components of these amorphous ground substances Two mucopolysaccharides have been isolated from normal tissues, one a sulfate-free complex polysaccharide acid which we named hyaluronic acid, the other the long known sulfate ester chondroitin sulfate

HYALURONIC ACID

Regarding the problem of the distribution of hyaluronic acid in the body, the presence of hyaluronate has recently been reported by many investigators on the basis of histochemical methods These methods employ metachromatic staining or other stains for high molecular weight carbohydrates before and after treatment with enzyme extracts having hyaluronidase activity There are obvious differences in the staining characteristics of tissues before and after enzymatic digestion In many instances the interpretation of these histochemical reactions leaves much to be desired For example, isolated hyaluronate does not stain metachromatically in concentrations below 1 per cent. Lison believed that only high molecular weight sulfate esters show true metachromasia Hyaluronic acid is not a sulfate ester, although it must be borne in mind that, with very few exceptions, samples of isolated hyaluronate do contain sulfate, in some preparations in rather high concentrations For example, a sulfur content of 1 per cent, as recently reported by Hadidian and Pirie, would represent 15 to 20 per cent of a monosulfate ester In fact, we have been able to obtain hyaluronate of very low sulfur content (that is, 0 1 per cent or less) only from synovial fluid and tumor fluids. Hyaluronate from umbilical cord usually contains considerable sulfate. Whether this sulfate is contaminating chondroitin sulfate, or hyalurono-sulfate, or one of the other known sulfate esters such as heparin or amyloid polysaccharide, is not known at present

The rigorous demonstration of hyaluronic acid still requires isolation and

chemical characterization. On this basis, *the presence of hyaluronate in* adult connective tissue is only certain in skin.

CHONDROITIN SULFATE

Chondroitin sulfate was first isolated from cartilage over seventy years ago by Schmiedeberg. Since then cartilage has served as the sole source of chondroitin sulfate. There are, however, significant differences between the chondroitin sulfate obtained from this source and that which has been obtained from other tissues. The concentration of chondroitin sulfate in cartilage is very much greater than that in loose connective tissue. In cartilage, chondroitin sulfate appears to be bound to a soluble collagen by a polar (i.e., salt) linkage rather than by a stable covalent bond. In loose connective tissue, on the other hand, chondroitin sulfate forms a true mucoid, that is, it is bound to protein by a stable linkage. The chondroitin sulfate of cartilage is relatively easily hydrolyzed by testicular hyaluronidase, while that of loose connective tissue, when isolated, appears resistant to the action of the same enzyme. As we pointed out several years ago, the optical rotation of cartilaginous chondroitin sulfate is different from that obtained from skin and umbilical cord. In loose connective tissue, chondroitin *sulfate thus far has been found in association with hyaluronic* acid, while in cartilage, hyaluronic acid seems to be absent.

Since the chondroitin sulfate of loose connective tissue is stably bound to protein, extraction with strong salt solution or urea does not yield the *polysaccharide; the latter is obtained only after the use of strong alkali* such as 0.5 normal sodium hydroxide. Extraction with weak alkali, such as 0.02 normal calcium hydroxide, in some instances does yield a protein complex from which, after treatment with strong alkali, the polysaccharide sulfate ester is obtained, but the mucoid is denatured. *Recently* we have obtained from heart valve a native mucoid containing a sulfate ester which appears to be chondroitin sulfate. Electrophoretically the mucoid preparation showed two components. The main component, which comprised about 75 per cent of the total, has a mobility at *pH* 8.6 of 8.1×10^{-5}. The carbohydrate content is approximately 25 per cent by weight. The protein component does not appear to be related to collagen. It remains to be determined whether this mucoid is antigenic and how it behaves toward enzymes.

COMMENT

The dynamic aspects of the problems related to these polysaccharide cement substances can be treated only briefly because of the scarcity of information. Nothing is known of either the mechanism of synthesis of these substances or the rate at which they are broken down and replaced in the body. The information which is available is mostly concerned with

enzyme concentrations have been shown to exert a profound physiologic effect. From this we have to assume that the serum protein fraction responsible for the in vitro inhibition is either absent in the subcutaneous tissue (which seems very unlikely) or that the whole system studied in vitro has no relation to the in vivo conditions.

Another factor is worth stressing concerning hyaluronidases of animal origin. We know something only of testicular hyaluronidases. We believe that enzymes depolymerizing and hydrolyzing both hyaluronate and the chondroitin sulfates in tissues other than testis do occur. Other workers have attributed our finding of hyaluronidase in the uveal tract, skin and spleen to bacterial contamination. But it would be difficult to explain in this manner the hyaluronidase activity of press juice of the cornea or of aqueous humor. Undoubtedly the concentration of such enzymes in the tissues is very low. The hyaluronate injected into the anterior chamber or intravenously into animals disappears rather rapidly, and in tissues like synovial fluid or synovial tissue the enzyme concentration may be too low to be detectable by our present methods. The normal turnover of the mesenchymal polysaccharides consequently may be assumed to be very slow. It naturally is possible that the degradation of these polysaccharides or their protein complexes has a nonhydrolytic pathway, but this possibility seems remote. The production of hyaluronate, and possibly of chondroitin sulfate, appears to be much faster than their removal, as evidenced by the pathologic accumulation of hyaluronate in the synovial sac and in other body cavities in certain tumors.

DISCUSSION

EDWARD W. DEMPSEY

Dr. Meyer has commented upon the importance of the connective tissue ground substances as sites of pathologic processes in the rheumatic diseases. The intercellular matrix of connective tissues is of great biologic importance in many other situations. Newly forming connective tissue exists as a loose syncytium of fibroblasts, the spaces or pores of which are filled with an interstitial fluid. During differentiation, one of several remarkable transformations occurs in this interstitial fluid. In collagenous or elastic tissue fibers appear within it. Calcium salts are deposited in the case of bone. Chondroitin sulfate is accumulated into the semirigid matrix of cartilage, and we are learning presently from Dr. Meyer's work that hyaluronic acid and probably other mucopolysaccharides are similarly accumulated in other locations. The interstitial fluid, the fibers and the ground substance matrix all seem to be in a state of dynamic equilibrium with the products of the cells and the substances transported by the blood stream. The physical character of the connective tissue, whether bone or tendon or loose connective tissue, is determined by the amount and kind of intercellular material rather than by differences in the organization of the cells themselves. Pathologically, too much, too little or an inappropriate matrix can cause serious embarrassment to the affected part.

The study of the ground substances has been undertaken largely from two related points of view. The first, exemplified by Dr. Meyer's investigations, concerns the qualitative and quantitative determination of the com-

ponent substances of the matrix. For such studies relatively large amounts of material are needed, and the original location of the extracted substances cannot be stated with microscopic accuracy. The second, depending upon histologic procedures, permits a more precise description of the relationships between the ground substances and the other morphologic structures These methods, however, lack the chemical precision which is desired. At their best they permit the localization of substances exhibiting one or more of the characteristic reactions of the compounds which have been isolated and identified.

The polysaccharides containing sulfuric acid exhibit metachromasia in solutions, and the regions from which these compounds have been extracted are also metachromatic when examined in histochemical preparations The sulfate-free hyaluronic acid is less reactive and is metachromatic only when tested in concentrated solutions However, in histochemical preparations, the ground substance is precipitated and dehydrated before staining Its local concentration is therefore high The metachromasia observed in vitreous humor, synovial fluid and elsewhere might be explained either by the presence of hyaluronates or by contamination with sulfate esters It should also be kept in mind that metaphosphates and silicates have been shown to induce metachromasia.

The sugar portion of the mucopolysaccharide complex, after oxidation in periodic acid, reacts with the Schiff reagent All mucopolysaccharides do not react with equal vigor Moreover, substances other than polysaccharides also give this reaction

Dr Meyer has mentioned the enzyme methods, and has commented that their specificity leaves much to be desired.

None of these three histochemical methods permits identification of mucopolysaccharides Nonetheless, applied together they can locate accurately substances which exhibit a peculiar staining quality characteristic of mucopolysaccharides, *which exhibit carbohydrate reactions like those of* mucopolysaccharides, and which are destroyed by enzymes capable of degrading mucopolysaccharides

No one method is perfect The chemical methods do not permit the accurate localization of the ground substances in highly complex tissues The histochemical methods achieve more satisfactory localization, but at best permit characterization rather than identification of the specific substances By applying the methods together, more can be learned than with one method alone.

THE RELATION OF CONNECTIVE TISSUE SUBSTANCES TO THE RHEUMATIC DISEASES*

CHARLES RAGAN

Clinically there are many dissimilarities between the three main groups of rheumatic diseases—rheumatic fever, rheumatoid arthritis and degenerative joint disease. In no way can a common pathogenesis be assumed, but the supporting structures—tissues of mesenchymal origin—are involved in all

RHEUMATIC FEVER

Rheumatic fever may involve practically any connective tissue in the body. Klinge showed that the first change in the rheumatic nodule was in the ground substance, with secondary changes in the fibrillar elements with infiltration of wandering cells The initiation of rheumatic fever is intimately associated with infection with the group A hemolytic streptococcus

no recurrence of rheumatic activity when the infecting group A streptococcus was an hyaluronidase-producing strain which did not produce the mucopolysaccharide Antibodies to various products of the streptococcus are found circulating during rheumatic fever, one being an antistreptococcal hyaluronidase. Attempts to confer antigenicity on hyaluronic acid have not been successful Thus most information on the relation of rheumatic activity to hyaluronic acid or hyaluronidase is exceedingly indirect.

The one characteristic feature of the joint lesions of rheumatic fever is their reversibility with full recovery on or without antirheumatic drugs,

that patients with rheumatic fever untreated with salicylate exhibited an increased spread with hyaluronidase when compared with controls In our experience, a rheumatic patient not under salicylates shows no greater response to the spreading reaction of testicular hyaluronidase than does the control. The mechanism of the inhibition of spreading by salicylate ingestion described by Guerra was not clear since a change in the substrate could scarcely be predicted to take place so rapidly and since salicylate inhibited hyaluronidase in vitro in only very high concentration, indeed, only at levels at which other biologically active proteins were denatured An in vivo metabolic product of salicylate, gentisic acid, recovered from the urine of patients receiving salicylate, was found to inhibit hyaluronidase in vitro when aged in an alkaline solution, and synthetic gentisic acid was found to have definite antirheumatic properties Quinone-hydroquinone systems, as represented by gentisic acid, are active biologic agents so it

cannot be maintained that the antirheumatic action of gentisic acid represents hyaluronidase inhibition or that rheumatic activity is related to hyaluronidase activity, but this serves as an hypothesis upon which further lines of investigation may be based

RHEUMATOID ARTHRITIS

In rheumatoid arthritis, involvement of the supporting structures, notably the joint lesions, is less reversible The first changes in the synovial structures are of a nondescript inflammatory character indistinguishable from other joint inflammations These changes are soon succeeded by an overgrowth of granulation tissue or poorly differentiated connective tissue. Changes in the cartilage may be looked upon as secondary to nutritional disturbances caused by this pannus The hyaluronic acid of the joint fluid of patients with rheumatoid arthritis has been found to be less highly polymerized than that obtained from normal joints, but there is an excessive amount of this low polymer mucopolysaccharide present One may perhaps infer from the presence of an increased quantity of this low polymer hyaluronic acid in the synovial fluid that the defect lies in the synthesis of this mucopolysaccharide rather than in its enzymatic degradation Nothing is known of the pathways by which these mucopolysaccharides are synthesized in vivo This disturbance in the biochemistry of hyaluronic acid may possibly be correlated by analogy with the granulation tissue of the pannus, which also does not reach the stage of a mature well differentiated connective tissue

Other changes seen in rheumatoid arthritis likewise involve the interfibrillar elements The lymphorrhages in the skeletal muscles and in the sheaths of nerves lie between the fibrous elements. The rheumatoid nodule is similar [illegible] nodule but there is usually an increased amount of necrosi[illegible] certain of the staining c[illegible] etiologic relationship between the group A *hemolytic streptococcus and rheumatoid* arthritis, such as exists in rheumatic fever, has not been shown and the action of salicylates on the joint symptoms of rheumatoid arthritis is apparently solely an analgesic one Thus there is no evidence, however indirect, that hyaluronidase activity plays any part in rheumatoid arthritis in contrast to rheumatic fever

DEGENERATIVE JOINT DISEASE

While in rheumatic fever the joint cartilage is not involved and in rheumatoid arthritis the involvement is probably secondary to the growth of pannus, in degenerative joint disease the primary defect is an involvement of joint cartilage In fact, cartilage throughout the body is involved in the process The change lies primarily in the matrix of the cartilage, with apparent degeneration of the chondroitin-sulfate-protein complex permitting the appearance of the fibrillar elements which, in normal cartilage, are embedded in the homogeneous matrix and are not visible on section This change is associated with the ageing process and is accentuated by increased stress and strain Changes in the cartilage of young growing animals induced by the administration of estrogens, thyroid hormones and the growth hormone of the pituitary, have been demonstrated but the applica-

tion of these findings directly to degenerative joint disease cannot be made at the present time

In summary, rheumatic fever, rheumatoid arthritis and degenerative joint disease involve supporting structures of mesenchymal origin There is fragmentary evidence that in rheumatic fever there may be increased activity of the enzyme hyaluronidase In rheumatoid arthritis, this enzyme is apparently not a factor but there may be an overproduction of defective connective tissue, both fibrillar and interfibrillar In degenerative joint disease, degeneration of the chondroitin-sulfate-protein complex of cartilage takes place in conjunction with ageing and is conceivably related to changes in hormonal production

* * *

THE PROTEAN NATURE OF THE CONNECTIVE TISSUE DISEASES*

WALTER BAUER, J. E GIANSIRACUSA AND J P KULKA

In recent years there has been an increasing tendency to speak collectively of rheumatoid arthritis, rheumatic fever, lupus erythematosus disseminatus, periarteritis nodosa, dermatomyositis, and generalized scleroderma as "connective tissue diseases" The demonstration of widespread morphologic alterations in the fibrous connective tissues has led to the concept that these diseases, protean in nature, may be related This is in sharp contrast t [illegible] distinct and unre [illegible] diseases are syste [illegible] acterized by involvement of tissues of mesenchymal origin

CLINICAL MANIFESTATIONS

Tabulation of the clinical manifestations of these diseases will serve to illustrate these points and stress the common features (see Table 59)

Constitutional symptoms, particularly weakness, easy fatigability, anorexia, weight loss and fever are seen in these entities Their presence in marked degree during the initial phases and before the onset of localizing symptoms indicates the systemic nature of these diseases Indeed, in the acute stages, many of these diseases may simulate an acute infectious process.

Vasomotor symptoms, varying in incidence and severity, are common to this group of diseases When present in pronounced degree as an early manifestation of the underlying disease the diagnosis of Raynaud's disease is frequently made

The symptom-complex, chorea, is almost always a manifestation of rheumatic fever, but has been observed in patients with lupus erythematosus disseminatus

The ocular symptoms, episcleritis, uveitis and scleromalacia perforans, are seen almost exclusively in rheumatoid arthritis

* A more detailed account of our experience with these diseases will be published later

The cutaneous manifestations of these diseases are often impossible to differentiate from each other. This is especially true of the erythemas of rheumatoid arthritis and rheumatic fever, the rash and telangiectasis of lupus erythematosus disseminatus and dermatomyositis, and the subcutaneous and cutaneous changes of dermatomyositis and scleroderma. Certain skin lesions, however, are frequently of diagnostic significance; these will be discussed later.

Hemorrhagic manifestations are common to all except scleroderma. They are most frequent in lupus erythematosus disseminatus and in this disease may be an expression of thrombocytopenia

Table 59 Clinical Manifestations of Connective Tissue Diseases

	Constitutional	Vasomotor	Chorea	Ocular	Skin	Purpura	Mucous membranes	Lymphadenopathy	Serositis	Cardiac	Hypertension	Pulmonary	Gastro-intestinal	Arthritis	Nodules	Muscles	Peripheral nerves	Eosinophilia	Renal	W.B.C.
Rheumatoid arthritis	+	+	O	[+]	+	+	O	+	+	+	O	O	O	[+]	[+]	+	+	+	⊕	↑↓
Rheumatic fever	+	±	[+]	±	+	+	O	O	[+]	[+]	O	+	+	[+]	[+]	±	O	O	±	[↑]
Lupus erythematosus disseminatus	+	+	±	±	[+]	[+]	[+]	+	[+]	[+]	+	+	O	[+]	[+]	+	O	O	[+]	[↑↓]
Periarteritis nodosa	+	±	O	O	+	+	O	+	+	+	[+]	[+]	+	[+]	+	[+]	[+]	[+]	[+]	[↑]
Dermatomyositis	+	+	O	O	[+]	±	±	+	±	±	O	O	[+]	[+]	+	[+]	O	+	±	↑
Scleroderma	±	+	O	O	[+]	O	O	O	O	[+]	O	[+]	[+]	[+]	O	+	O	O	O	N

The ± [illegible] cated grossly by the size of the arrows; ↑ = leukocytosis, ↓ = leukopenia

Mucous membrane lesions, a frequent finding in lupus erythematosus disseminatus, are rarely seen in the other diseases.

Generalized lymphadenopathy, seen most often in rheumatoid arthritis and lupus erythematosus disseminatus, may be an early and prominent systemic feature of all these diseases.

Serositis is a manifestation common to all save scleroderma

Various types of cardiac lesions are demonstrable in each of these diseases. Myocarditis is common to all Valvulitis is seen only in rheumatic fever, lupus erythematosus disseminatus and rheumatoid arthritis, in that order of frequency. Clinical differentiation of these latter diseases on the basis of the presence or absence of organic murmurs is not warranted, however, the morphologic features of the valvulitis in each of these diseases are usually distinctive.

[illegible] in the case of peri-

[illegible] *onary manifestation*

seen in some of these diseases will be discussed later The migratory pneumonitis of rheumatic fever and lupus erythematosus disseminatus is clinically indistinguishable.

The chief symptoms referable to the gastro-intestinal tract are pain in rheumatic fever and periarteritis nodosa and disturbed motility in dermatomyositis and scleroderma

Articular symptoms, varying in frequency and severity, are common to all these diseases and may in some instances be clinically indistinguishable This is particularly true of lupus erythematosus disseminatus, the articular manifestations of which frequently simulate those of rheumatic fever and occasionally those of rheumatoid arthritis

Subcutaneous nodules, the most significant of the cutaneous lesions in rheumatoid arthritis and rheumatic fever, show relatively specific morphologic alterations Clinically similar nodules are seen occasionally in the other diseases. Usually they are readily distinguished from those of rheumatoid arthritis and rheumatic fever Occasionally they exhibit the features of both rheumatoid arthritis and rheumatic fever nodules

Manifestations referable to muscles are seen in all Even in the absence of muscular symptoms, inflammatory foci can sometimes be demonstrated

The peripheral nerve involvement of periarteritis nodosa is an important diagnostic sign The demonstration of focal accumulations of inflammatory cells in the peripheral nerves of rheumatoid arthritis, rheumatic fever, lupus erythematosus disseminatus and dermatomyositis is additional evidence that these diseases are systemic in nature

Leukocyte counts often deviate significantly from normal in all except scleroderma Impressive eosinophilia is frequent in periarteritis nodosa and occasionally seen in rheumatoid arthritis

Renal disease is a prominent feature of lupus erythematosus disseminatus and periarteritis nodosa Occasionally there are urinary abnormalities in rheumatic fever and dermatomyositis Renal involvement in rheumatoid arthritis should always lead one to suspect amyloidosis, though very rarely it is a manifestation of the disease

Paralleling these clinical similarities are the morphologic alterations connective tissues Detailed discussion of this subject is not within t scope of this presentation

DIAGNOSTIC FEATURES

For aid in diagnostic orientation, the squares in Table 59 call atten to the prominent or characteristic features It will be noted that these tures may overlap to some degree, yet their presence suggests the diag or limits the diagnostic possibilities In the latter instances continued servation usually enables one to establish the diagnosis

Rheumatoid arthritis is characterized by progressive, symmetric artl Usually the pattern of development and the type of articular involve result in a clinical entity which can be recognized readily In the so- prodromal stage and in atypical forms the presence of ocular involve most often uveitis, or the presence of subcutaneous nodules may se the clue to the final diagnosis The subcutaneous nodules, although cl similar to those seen in rheumatic fever and lupus erythematosu minatus, present relatively specific pathologic alterations Very r renal disease a manifestation of rheumatoid arthritis Renal abnor

may indicate the presence of amyloidosis or require consideration of lupus erythematosus disseminatus or periarteritis nodosa.

In rheumatic fever, cardiac involvement (usually endocarditis or myocarditis, less often pericarditis) is the most significant manifestation Disturbances in auricular-ventricular conduction time are frequent but not diagnostic because they are seen occasionally in rheumatoid arthritis and lupus erythematosus disseminatus. The arthritis is migratory in nature and rarely causes persistent inflammation of periarticular structures Microscopic examination of nodules, if present, usually permits differentiation from rheumatoid arthritis and lupus erythematosus disseminatus The presence of chorea is presumptive evidence of rheumatic fever The same is true of erythema marginatum The infrequent abdominal pain and the migratory pneumonitis are not diagnostic A leukocytosis is usually present, a leukopenia is distinctly unusual and suggests the possibility of lupus erythematosus disseminatus.

Criteria for the diagnosis of lupus erythematosus disseminatus are not easily stated The presence of a typical skin rash, serositis, arthritis, leukopenia and renal disease in a patient with fever and other constitutional symptoms makes the diagnosis highly probable. However, the clinical picture may not be present in its entirety Some of these manifestations may be absent in an individual case, some may be present only transiently, others may appear only in the last few weeks or days of life The latter statement is particularly true of the skin and renal involvement We would hesitate to make a diagnosis of lupus erythematosus disseminatus in the absence of

to different

festations a...

Though several of these diseases exhibit hemorrhagic phenomena, thrombocytopenic purpura is seen only in lupus erythematosus disseminatus. Serositis without valvulitis, common in lupus erythematosus disseminatus, is seen also in rheumatoid arthritis and periarteritis nodosa, in rheumatic fever both serositis and valvulitis are usually present, though the former cannot always be demonstrated clinically. The presence of a leukopenia favors lupus erythematosus disseminatus The articular involvement may be indistinguishable from that seen in rheumatoid arthritis and in rheu-

and leukopenia

The diagnosis of periarteritis nodosa, even when suspected, may be difficult to establish A history of serum sickness or sensitivity to sulfonamide compounds is not a prerequisite The diagnosis is suggested by various combinations of ... ph-

eral neuritis, ab... ko-

cytosis and eosi... res

all present. A single muscle biopsy may corroborate the clinical impression but, if negative, does not rule out the diagnosis The central nervous system findings are so varied that they are of no aid in differentiation. The articular involvement may be acute and migratory, however, it can simulate rheumatoid arthritis occasionally.

Dermatomyositis, once well established, is characterized by emaciation,

induration of the subcutaneous tissues, marked weakness, atrophy and contractures of skeletal muscles and frequently calcinosis Disturbances in motility of the gastro-intestinal tract, particularly the esophagus and small bowels, are noted occasionally. Early in the disease, moderate to marked constitutional symptoms, muscle weakness and wasting, and articular symptoms are often the only manifestations In such patients only the passage of time will permit the differentiation of dermatomyositis from rheumatoid arthritis Occasionally the presence of these symptoms plus a malar erythema and slight albuminuria will closely simulate the clinical picture of lupus erythematosus disseminatus Even more difficulty is encountered in the differentiation of dermatomyositis from scleroderma The pathologic features of these two diseases may so overlap as to make a single diagnosis seem inadequate

The typical case of scleroderma can be recognized at a glance The tight, waxy, adherent skin with areas of pigmentation and depigmentation is characteristic The scirrhous process may involve the heart, the clinical manifestations being progressive cardiac dilatation and congestive failure It may result in pulmonary fibrosis Disturbances in the motility of the gastro-intestinal tract are much more common than in dermatomyositis and occasionally disproportionate to the degree of skin involvement Before the appearance of characteristic changes in the integument, the presence of vasomotor symptoms, articular pain and stiffness and muscle weakness may suggest rheumatoid arthritis In such instances the passage of time is usually of diagnostic aid In an occasional patient typical rheumatoid arthritis and sclerodermal changes may develop simultaneously As already mentioned, the differentiation of dermatomyositis from scleroderma is even more difficult.

CASE REPORTS

As indicated above, the clinical features considered characteristic of one or another of these diseases may overlap to such an extent that diagnosis is difficult and at times impossible Occasionally one of these diseases seems to supersede another Rarely, the pathologic features characteristic of two or more different diseases occur coincidentally Some of these diagnostic problems are illustrated

In the first case the l[illegible] ical feature suggested another diagn[illegible] and subsequent events.

Case I This patient, a nineteen-year-old boy, was first seen in 1934 because of persistent symmetric swelling of metatarsophalangeal joints, ankles, wrists and finger joints of two years' duration Additional findings were subcutaneous nodules, weight loss, low-grade fever, generalized lymphadenopathy, splenic enlargement and a moderate leukocytosis A diagnosis of rheumatoid arthritis was made One year later the findings and interpretation were the same except for a well marked eosinophilia Biopsy of a recent nodule showed a lesion indistinguishable from

tissues there was a patchy permeation with fibrinoid material

During the next five years the patient improved gradually, and in 1940 he was taken into the United States Army Shortly thereafter, marked swellings of the

legs and persistent albuminuria appeared. Since then, he has had occasional edema of the ankles, mild articular symptoms, moderate lymphadenopathy, persistent albuminuria and hematuria. The eosinophil count is normal.

From this case, it would appear that periarteritis nodosa and rheumatoid arthritis may simulate one another for a period of years.

In the next case, a long period of observation and biopsy served to define the diagnostic problem.

Case II. The patient, a twenty-nine-year-old man, was first seen in 1942, complaining of progressive symmetrical arthritis of large and small peripheral joints of two years' duration. The clinical picture was entirely consistent with rheumatoid arthritis until six months before admission. At that time, the appearance of a skin rash, an increase in constitutional symptoms and the presence of pleurisy suggested the possibility of lupus erythematosus disseminatus. On admission the additional findings of generalized lymphadenopathy, leukopenia, urinary abnormalities and a skin biopsy confirmed the diagnosis.

A second biopsy from the proximal interphalangeal joint of the right index finger showed, in addition to a nonspecific chronic synovitis, a 4-mm lesion which, though atypical, was consistent with a rheumatoid or rheumatic fever nodule Here the three characteristic zones of a rheumatoid nodule were apparent a central area of fibrinoid alteration and necrosis, an intermediate layer of palisaded mesenchymatous cells, and a nonspecific chronic inflammatory reaction at the periphery. However, the well developed fibrinoid lattice and relatively large number of polymorphonuclears were more suggestive of a rheumatic fever nodule

During the year following the biopsy, edema, marked albuminuria and hypoalbuminuria appeared In the last five years the rash has faded, the edema has subsided and articular symptoms have been minimal. Significant albuminuria has persisted

This case illustrates the fact that lupus [illegible] simulate rheumatoid arthritis for a time. [illegible] *and the renal involvement were the firs* [illegible] The presence of a lesion having features of both rheumatoid arthritis and rheumatic fever nodules suggests the possibility that these three diseases may be related

Even more instructive is the type of case in which a complete postmortem examination fails to narrow the diagnosis to a single member of the group of diseases under discussion An example is the following case [1]

Case III A twenty-nine-year-old housewife first complained of fatigue, cough, loss of weight and intermittent [illegible] epistaxis and ecchymoses and fever [illegible] the onset of symptoms because [illegible] findings were papular, urticaria-like lesions with denuded surfaces on the face and arms, many petechiae and ecchymoses, a marked thrombocytopenia, prolonged bleeding and clotting times and a leukocyte count of 4000 Following a splenectomy, the bleeding and clotting times and the leukocyte count returned to normal, but the platelet count remained low. During the next three months, the rash persisted, the articular symptoms became more severe, the hemorrhagic phenomena recurred and generalized lymphadenopathy and albuminuria appeared The leukocyte count remained normal. The terminal events were a rise in nonprotein nitrogen, continued fever and coma The final diagnosis was lupus erythematosus disseminatus

At autopsy the most striking finding was widespread polyarteritis nodosa. The lesions involved some medium-sized coronary arteries and the arcuate arteries of

of lupus erythematosus disseminatus was the presence of a focal glomerulitis, but similar renal lesions have been observed also in periarteritis nodosa [2]

In this case, adherence to existing diagnostic criteria would seem to necessitate two diagnoses, lupus erythematosus disseminatus and periarteritis nodosa If it were not for the widespread involvement of arteries as well as arterioles and the well marked periarterial inflammatory cell in-



Fig 120 Kidney, showing segmental necrotizing panarteritis of the arcuate arteries (×50)

filtration, the diagnosis of *lupus erythematosus disseminatus* would be adequate Thus the clinician may ask the pathologist· How often is the distinction between these diseases made on a quantitative rather than a qualitative basis?

The following case[3] exhibited both the clinical and pathologic features of two of the entities under discussion

endarteritis and segmental necrotizing arteritis in the kidneys with resulting thrombosis and focal cortical infarction

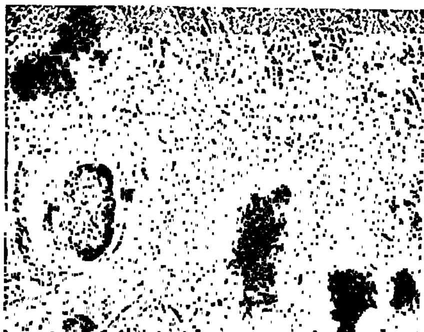


Fig 121 Myocardium, showing four miliary extravascular granulomas as well as two similar submiliary lesions lying respectively within and adjacent to the wall of a medium-sized artery with segmental granulomatous arteritis (×200)

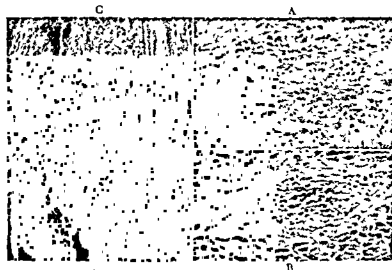


Fig 122 Epicardial artery with classical polyarteritis nodosa (×200)

This case suggests a relationship between dermatomyositis and generalized scleroderma It seems unlikely that two such rare diseases should develop simultaneously in the same patient Either these clinical entities represent manifestations of the same disease process or one may closely simulate the other. It is of interest that a necrotizing angiitis was also present.

The last case[4] shows the most varied morphologic lesions of all

Case V. The patient, a twenty-one-year-old man, developed bronchial asthma one year prior to admission On the day before entry he experienced severe hypogastric pain and increasing dyspnea On entry he had the signs and symptoms of severe heart failure The leukocyte count was 17,000 with 11 per cent eosinophils. He died on the same day despite intensive therapy



[illegible]

At autopsy miliary and submiliary lesions were scattered throughout the viscera The majority of these lesions were so-called "allergic granulomas" with central areas of fibrinoid necrosis surrounded by proliferating and, at times, radially palisaded mesenchymatous cells, they showed a striking tendency to be situated within or adjacent to the walls of blood vessels (see Fig 121) In addition, however, there were lesions which seemed to represent transitional forms between classical polyarteritis nodosa and the intramural granulomas on the one hand (see Fig 122) and between identical extravascular granulomas and isolated Aschoff bodies on the other (see Fig. 123)

The presence in this case of an entire spectrum of lesions varying from focal necrosis to predominantly proliferative reactions and involving both blood vessels and extravascular mesenchymatous tissues suggests the possibility that these morphologically divergent lesions may be manifestations of a similar tissue injury differing only in intensity and site of action.

Despite the fact that rheumatoid arthritis, rheumatic fever, lupus erythematosus disseminatus, periarteritis nodosa, dermatomyositis and scleroderma usually conform to distinct disease patterns, it is apparent that they have many overlapping features. The existence of cases with pathologic lesions characteristic of two or more of these diseases further suggests a relationship.

The exact nature of this relationship with regard to etiology and pathogenesis is unknown We agree with Klemperer[5] and Duff,[6] who have aptly pointed out that tissue may react in a similar way to many different types of injury and only the final step or steps in the chain of pathogenic cause and effect need be similar to account for the morphologic resemblance of the lesions Since these diseases usually differ in clinical pattern and prognosis, the generally accepted terminology serves a useful purpose. Cases such as the one cited, however, suggest that some of the accepted diagnostic criteria are arbitrary. We should like to emphasize that rigid adherence to these criteria may obscure clues pointing to common pathogenic mechanisms Such clues are of importance in orienting the investigative approach to these diseases

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EXPERIMENTAL ARTHRITIS

PLEUROPNEUMONIA-LIKE ORGANISMS AND THEIR POSSIBLE RELATION TO ARTICULAR DISEASE

LOUIS DIENES AND HOWARD J WEINBERGER

A few years ago attention was called[1] to the fact that infectious processes produced in mice with various strains of pleuropneumonia-like organisms resemble in some respects rheumatic fever and rheumatoid arthritis in humans Articular involvement is seen also in other animal species infected with similar organisms Efforts to prove that these organisms are connected with the rheumatic diseases in man so far have failed, but observations concerning their properties and nature have brought out certain facts of great importance in the study of infectious diseases It has become apparent that these organisms do not constitute an independent class or order of microorganisms different from bacteria, like the *Actinomyces*, for example, but that they are growth forms of bacteria comparable to smooth and rough strains[2, 3]

Under appropriate conditions many of the common pathogenic and saprophytic bacteria are transformed with ease into pleuropneumonia-like forms The pathogenic properties of these changed bacterial forms have not been adequately studied as yet In animals organisms with similar morphology are important pathogens They also occur in man and probably produce disease. This radical transformation of bacteria will probably further our understanding of certain infectious diseases It is of special interest in the study of rheumatic fever Some relationships of the streptococcus to this disease have been established, but the streptococcus cannot be demonstrated in the lesions nor do the latter correspond to streptococcal lesions The possible presence of streptococcus in an altered form with special affinity for the heart, joints and other structures becomes a reasonable supposition and deserves careful study

MORPHOLOGY AND REPRODUCTION

The pleuropneumonia group of organisms differs from the usual bacteria in many respects[4] The size of the organisms is much smaller By filtration through gradocol membranes it has been determined that the animal pathogenic strains and those isolated from sewage and earth contain reproductive granules between the sizes of 0 1 and 0 2 micron There is, however, a difference between the viruses and pleuropneumonia-like organisms in regard to size In the case of viruses most of the organisms are small and pass through appropriate filters The size of the pleuropneumonia-like organism varies and only a portion of them is very small A similarity to the viruses is that the pleuropneumonia-like organisms usually are not visible in tissues or exudates In the highly infectious edema fluid of the lung in infected cattle, the pleuropneumonia-like organisms cannot be discerned with the usual staining methods For a long time the organisms were not detected even in the colonies grown on agar Like the protozoa, these or-

ganisms are so fragile and vulnerable that they are destroyed and unrecognizable in a dry smear

Examination with appropriate methods showed that the cultures consist of organisms of varying size and shape (Fig 124). Tiny granules and round forms varying in size from less than 1 micron to 5 or 10 micra are present in the cultures. Some cultures contain filaments of variable length The small forms multiply by fission like bacteria, while the large round forms reproduce many small ones by multiple germination or by the breaking up of their protoplasm This multiplication by swelling and differentiation into small forms is characteristic of the pleuropneumonia group

The distinctive characteristics of the pleuropneumonia group, their small size, the fragility of the organisms and the presence of a reproductive

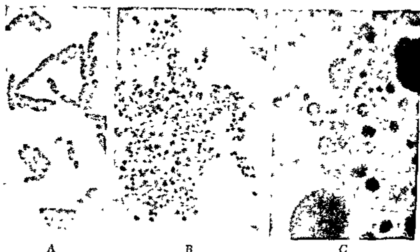


Fig 124. Morphology of typhoid bacilli and of the L type cultures A Typhoid bacilli, stained agar preparation (×2300) B L type culture from typhoid bacilli grown in broth, stained with crystal violet mounted in saline (×2300) C L type colonies from typhoid bacilli, impression preparation, stained with thionin mounted in saline, very high magnification (×3800)

process different from binary fission, suggest that this group forms a class or order of microorganisms different from bacteria This is the usually accepted opinion concerning their nature and classification At closer examination the dividing line between bacteria and the pleuropneumonia group is less distinct Some bacterial strains belonging to various species and families show a pleomorphism and a multiplication process similar to those of the pleuropneumonia group The swelling of bacteria into large forms and their subsequent breaking up into the usual small ones has been observed in *B coli*[5] and in *Proteus* and *Bacteroides*[3, 6]

The difference between the pleuropneumonia group and bacteria is not qualitative but is one of degree Certain properties and processes which are observed rarely in bacteria are common in the pleuropneumonia group The most significant observation concerning the relationship of these two groups of microorganisms is that cultures similar in morphology and physical properties to the pleuropneumonia group can be isolated from many bacterial cultures Examined under appropriate conditions, almost all gram-

negative bacilli produce such cultures. They have been isolated in pure growth from cultures of *Streptobacillus moniliformis*,[7] *Bacteroides*, *Proteus*, typhoid bacilli,[3, 6, 8] *Salmonella*, dysentery, *Hemophilus influenzae* and from several species not fully identified, including a gram-positive spore-bearing bacillus.[9] It seems to be a general property of bacteria that under certain conditions they grow in a form and possess properties corresponding to the pleuropneumonia group. The morphology of these cultures is so similar that, without knowing their origin, it cannot be determined whether they were isolated directly from the specimens as pleuropneumonia-like organisms or obtained from bacteria.

FACTORS AFFECTING DEVELOPMENT

Pleuropneumonia-like colonies obtained from bacilli have been most thoroughly studied in *Streptobacillus moniliformis*, *Bacteroides* and *Proteus* cultures.[2, 10] Their nature is most clearly apparent in *Proteus*.[1] In this species pleuropneumonia-like colonies develop in the cultures under various conditions interfering with normal growth. Refrigeration of the cultures, growth inhibition exerted on one *Proteus* strain by another, and exposure to certain chemicals may induce their development. Penicillin incorporated in appropriate media transforms the whole culture into pleuropneumonia-like growth. While this culture is similar morphologically to the pleuropneumonia group, many of its properties indicate its identity with *Proteus*. Serologically they are closely similar to the parent strains and they exhibit the most distinctive metabolic activity of *Proteus*, urea fermentation. Even after many months of cultivation in the pleuropneumonia-like form, the cultures return readily to the usual bacillary forms of *Proteus*. Similar observations have been made with *Streptobacillus moniliformis* and *Bacteroides*.[8] The pleuropneumonia-like cultures isolated from the bacilli remain similar in serologic properties and in some of their distinctive metabolic properties to the parent bacilli, and under appropriate conditions they regain the usual bacillary form. It is apparent that the pleuropneumonia-like organisms are not accidental contaminations of the cultures or parasites of the bacilli but that they are a growth form of the bacillus which, under favorable conditions, returns to the usual bacillary form.

These peculiar growth forms of bacteria present many interesting characteristics in addition to their small size and their special reproductive process (Tables 60 and 61). They arise from the bacteria when, for some unknown reason, normal reproduction is disturbed. In addition to the effect of penicillin, autolysis of the culture is the most common cause of the development of these forms. Autolysis results from the antagonistic substances produced by the metabolism of the bacteria. The bacilli stop multiplying and die off, but some continue to grow in the pleuropneumonia-like form. In the case of typhoid bacilli these forms are produced during lysis by antibody and complement.[11] If mixtures of the bacilli, antibody and complement, incubated for varying periods of time, are transferred to appropriate media, pleuropneumonia-like colonies develop on the plates for a certain period following lysis of the bacilli. The pleuropneumonia-like cultures so obtained are similar in every respect to those obtained from the bacilli with penicillin. A bacteriostatic agent, carboxymethoxylamine, has the same effect as penicillin although to a slighter degree. The resistance to penicillin of the pleuropneumonia-like forms isolated from bacteria is

very high, regardless of whether they were isolated with the help of penicillin or with immune serum or whether they occurred spontaneously in the culture Their resistance to other antibiotics is not marked. Another characteristic of such cultures is that they grow slowly, often continuing to grow for several weeks. The center of the colony often autolyzes while the periphery continues to grow. All strains of pleuropneumonia-like organisms grow better on agar than in broth, and penetration into the surface of the agar seems necessary for abundant development of the cultures. In many

Table 60 Sugar Fermentation Reactions of L Strains

ORGANISM	DEXTROSE	MALTOSE	LACTOSE	SUCROSE
Salmonella typhosa L	Acid	Acid	No change	No change
S typhimurium L	Acid, gas	Acid, gas(?)	No change	No change

Table 61. Certain Properties of L Type Cultures

ORIGIN	DEVELOPMENT	GROWTH REQUIREMENTS	SEROLOGIC PROPERTIES	REVERSION
Streptobacillus moniliformis	Spontaneous, penicillin	Animal protein agar, hard and soft, aerobic, anaerobic	Similar to bacillus	Freshly isolated strains in broth
Bacteroides	Spontaneous; penicillin	Animal protein agar, hard and soft, anaerobic		Prolonged cultivation in broth
Proteus	Refrigeration, exposure to distilled water, penicillin	Animal protein agar, soft, aerobic, anaerobic	Similar to bacillus	On agar and in broth, 1 day to several weeks
Salmonella typhosa	Penicillin, antiserum	Animal protein agar, soft, anaerobic	Similar to bacillus	

cases the presence of fresh animal protein is necessary for their growth even though it is not required by the parent organism. In all cases studied the usual pathogenic actions of the bacteria seem to disappear when they are transformed to the L form

The return of the L form into the usual bacterial form varies with the species from which it is derived In some cases, the *Proteus*, for example, it occurs regularly within a few days. In *Bacteroides* it is necessary to keep the cultures for several weeks to observe the reversion Thus far it has not been observed in typhoid bacillus, although the serologic similarity of the bacillus and the pleuropneumonia-like forms indicates that in this case also they are a growth form of the same organism The inability to regain the usual bacillary forms in many cases makes it difficult to determine whether a pleuropneumonia-like organism isolated either from an animal or a human being is an independent organism which occurs only in that form or is a growth form of a common bacterium.

OCCURRENCE IN MAN

In human beings pleuropneumonia-like organisms can be cultivated most easily from the genito-urinary tract of females.[12] Positive cultures are obtained in one examination in about 30 per cent. The frequency of their occurrence varies considerably according to the condition of the mucous membranes. Klieneberger-Nobel[13] found such organisms in only 1 per cent of healthy women preceding childbirth, while the incidence was over 40 per cent in a gynecologic ward. In inflammatory processes extending from the genitals into the pelvis or in Bartholin cysts, they may be present in pure culture or mixed with other bacteria. They are rarely found in the urine of females. In males, pleuropneumonia-like organisms are most often present in the urethra. In one group of young service men, for example, the incidence of these organisms was found to be over 30 per cent, and they were often present in apparently normal urethras. Their incidence in the average hospital patient without genito-urinary symptoms is low. They are found more often in nongonorrheal urethritis and prostatitis. The most interesting group of patients in which the pathogenic effect of these organisms is suggested is that with "abacterial" cystitis. Twenty cases were examined in *one series and in eighteen of them pleuropneumonia-like organisms were* recovered. There does not seem to be complete agreement between the persistence or disappearance of clinical symptoms and the presence or absence of these organisms. For this reason caution is necessary in attaching etiologic significance to them. In some cases of nonspecific urethritis and prostatitis and of "abacterial" cystitis in which pleuropneumonia-like organisms are present, polyarthritis develops. This observation is sufficiently constant to suggest a similar etiology of both local and general symptoms. The fact that in animal diseases the pleuropneumonia group shows an affinity for the joints is very suggestive that the pleuropneumonia-like organisms found in the genito-urinary system are responsible for the polyarthritis.

Except for material from the genito-urinary tract and two joint fluids in cases with arthritis complicating the genito-urinary involvement, pleuropneumonia-like organisms have not been isolated from any other source except when penicillin was used in treating the patient or was added to the culture media. In patients treated extensively with penicillin these organisms have been isolated from the blood, spinal fluid, sputum, pleural exudate, paronychial pus and from the intestinal mucosa. If penicillin is added in appropriate amounts to the plates used for cultivation, pleuropneumonia-like organisms can be recovered from the throats of 75 per cent of normal persons. The role of penicillin is probably to eliminate bacterial growth and to give better conditions for the growth of pleuropneumonia-like organisms. It is probable also that the pleuropneumonia-like organisms are produced from the bacteria by the presence of penicillin on the mucous membranes or in the lesions as in the culture media. Pleuropneumonia-like organisms may occur in almost all organs, although we do not know whether they are distributed in the pleuropneumonia-like form or arise locally from the bacteria.

The pleuropneumonia-like organisms isolated from human beings certainly do not belong to a single species. There are persistent differences in their nutritional requirements and in morphologic and serologic properties between the strains. It has been pointed out that it is impossible to decide

whether they originate from bacteria or are independent organisms. Identification of these strains is still unsatisfactory, as is the actual determination of the presence of these organisms. The method of cultivation which most often gives positive results is evidently unsuccessful in many cases In some cases of abacterial cystitis, for example, we can culture only a few dozen tiny colonies no longer than 10 micra in diameter and cannot keep them growing in subcultures In many cases it is impossible to keep the pleuropneumonia-like colonies developing from bacteria growing in subculture. The pathogenic strains seem to be strictly adapted to a certain host and transfer to laboratory animals cannot be used for their identification. Inoculation into embryonated eggs results often in a poor growth or no growth at all The results obtained thus far in culturing pleuropneu- [illegible]

COMMENT

In 1934 only two members of the pleuropneumonia group were known The introduction of a new staining technique made it possible for Klieneberger to discover similar organisms in various animal species and sources and also in a bacterial culture It has necessitated long experimentation to find the techniques by which such organisms can be isolated from cultures of many gram-negative bacteria and from a few gram-positive ones. With improving methods the continuous widening of the spectra of bacterial species in which pleuropneumonia-like organisms occur is suggestive that all bacteria may produce such forms and that it may be only a matter of developing proper techniques to find them in gram-positive cocci It is hoped that their demonstration in pathologic processes will be more successful in the future and that the evidence for their pathogenicity in joint disease will be more conclusive

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DISCUSSION

THOMAS M BROWN

During the past ten years Dr Dienes has contributed extensively to our knowledge of human L organisms and it has become apparent that there are a great many differences in the behavior and the biologic characteristics between human and animal strains One should be conscious of these differences, since they may explain the discrepancy which exists between the readily induced arthritis in animals by animal strains and the present uncertain relationship of human strains to human articular disease

Dr. Dienes has described human strains characterized by extremely minute colonies Such colonies have not been isolated from animals The inability to subculture certain human strains has not been encountered with animal strains Dr Dienes has observed that certain bacteria found in man are capable of in vitro transformation into pleuropneumonia-like forms under certain conditions The only microorganism of animal origin known to be capable of transformation into the pleuropneumonia-like form is *Streptobacillus moniliformis*, an organism pathogenic for both animal and man Broth cultures of human strains have shown neither the characteristic faint clouding nor the bizarre pleomorphism of the animal strains described by Sabin Positive cultures have no doubt gone unrecognized by failure to note this difference Most human strains prefer anaerobic conditions, a point which Dr Dienes has observed and in which we concur Animal strains grow well under aerobic conditions In addition, arthritis has not been produced in animals with human strains

Both animal and human strains have the following properties in common unique colony morphology, minute reproductive particle size which will pass bacterial filters, susceptibility to gold salts, and resistance to sulfonamides and penicillin

The variety of causative factors in the transformation and the altered pathogenicity make it imperative to seek methods to determine the possible significance in human disease We have been particularly interested in the effect of various substances on human L organisms in vivo By this means it may be possible to detect the cause and effect relationship Dr Dienes and his coworkers have observed the effect of streptomycin on L organisms in vivo with varying results They have reported that in a case of nonspecific urethritis from which L organisms were recovered, myochrysine had no effect on the course of the disease

We have studied the in vivo effect of myochrysine on L organisms obtained from prostatic secretions in cases of rheumatoid arthritis One case in this group was studied for eighteen months Fourteen successive cultures of prostatic secretion were positive for anaerobic L organisms These were obtained during and after the entire course of intensive gold therapy which was followed by a clinical remission The patient ultimately developed a toxic skin reaction and gold therapy was discontinued Three months later there was a relapse of the rheumatoid arthritis Aureomycin therapy was instituted to determine its possible effectiveness on the L organisms All cultures following therapy were negative for pleuropneumonia-like organisms There were four such cultures over a three-month period Similar

disappearance of L organisms following aureomycin therapy has been noted in a total of eight cases.

In vitro activity of aureomycin on a strain of L organisms has been demonstrated by Paine and his collaborators. In vivo effectiveness has been noted by Collins and his coworkers in a case of nonspecific urethritis. We have been able to confirm these findings of the in vitro effect of aureomycin on human L forms and their rapid disappearance, with coincident clinical improvement, in a case of non-specific urethritis with aureomycin. Kuzell and his associates have observed the effect of aureomycin on rat arthritis produced by the L_4 strain of pleuropneumonia-like organisms. The response was comparable to that obtained with gold salts.

It was interesting to observe the clinical course of those patients in whom the L organisms disappeared under aureomycin therapy. Doses less than 1.0 gm per day were sufficient to eliminate L organisms from the genitourinary tract, but no significant clinical effect was noted. In several instances L organisms reappeared when aureomycin in this dosage was discontinued. Objective clinical response was noted, however, when aureomycin was increased to 2.0 gm per day. There was an initial mild exacerbation of symptoms in a number of the cases treated, comparable to that sometimes observed in our gold-treated cases.

Seventeen patients representing a wide variety of rheumatic diseases were treated with aureomycin. The clinical manifestations were those of rheumatoid arthritis, rheumatoid spondylitis, chorea, erythema nodosum, and rheumatic fever. Pleuropneumonia-like organisms were recovered from the genitourinary tract in seven of these seventeen patients. All patients responded equally well irrespective of the presence or absence of culturable L organisms.

At the present time the important problem is to establish the possible relationship of pleuropneumonia-like organisms to articular disease. The property of aureomycin to eliminate L organisms from the genitourinary tract, which gold does not possess, provides a means which may aid in the clarification of this problem. Only prolonged clinical trial will determine possible therapeutic usefulness.

CHEMOTHERAPEUTIC TRIALS IN EXPERIMENTAL POLYARTHRITIS OF RATS*

WILLIAM C. KUZELL, GRACE M. GARDNER, DE LOREZ M. FAIRLEY AND HELEN B. TRIPI†

As long as the causative factors of rheumatoid arthritis are obscure empiric treatment is necessary. No exact counterpart of rheumatoid arthritis has been produced in lower animals since no infective microbe or metabolic substance or disturbance has yet been discovered to produce in them a strictly comparable disease state The work of Selye[1] suggested that a disease state somewhat similar could be produced in rats which had had unilateral nephrectomy and which were given huge doses of desoxycorticosterone acetate prior to being exposed to cold However, we were unable to confirm Selye's claims

EXPERIMENTAL POLYARTHRITIS IN ANIMALS

On the other hand various workers in this country, England and elsewhere have been able to reproduce a polyarthritis in mice and rats using the L_4 strain of pleuropneumonia-like organism which has been isolated from naturally occurring arthritis in these rodents[2-5] Similar microbes have also been isolated in various diseases of sheep, cattle, dogs and guinea pigs. Human strains of pleuropneumonia-like organism have been isolated by us and by others[6] from urethral discharge, conjunctival lesions and joint fluid of patients with Reiter's syndrome, although no definitive proof has been presented implicating these microbes as the sole causative agent Dienes and his associates[7, 8] have repeatedly isolated pleuropneumonia-like organisms from the genital tract in many women with rheumatoid arthritis.

PREVIOUS STUDIES IN THERAPY

A point of considerable interest stems from the fact that in rats and mice this polyarthritis may be prevented and cured by the use of gold salts—agents which have been accorded some measure of success in the empiric therapy of rheumatoid arthritis of man Using the preventive and curative actions of gold compounds in the polyarthritis of rodents as a standard of
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a [illegible] d Warren[11]
showed effective preventive and curative effects with calcium aurothio-

* From the Department of Pharmacology and Therapeutics, Stanford University School of Medicine, San Francisco, California This work was supported, in part, by contract with the Office of Naval Research, U S Navy Department, and, in part, by the Stern and Bullard Funds for Experimental Arthritis

† With the technical assistance of Pelagio S Tabar

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showed that there was a slight preventive action exerted by neoarsphenamine in the arthritis of mice Sulfanilamide, sulfapyridine, sodium salicylate and lithium antimonyl tartrate were without effect. Sabin and Warren[11] showed effective preventive and curative effects with calcium aurothio-

malate Powell, Jamieson and Rice[12] showed that streptomycin was effective in preventing the polyarthritis of rats, whereas they had previously shown[13] that penicillin was ineffective Snow and Hines[14] showed that ligation of the common bile duct in rats before or twenty hours after the injection of L_4 organisms delayed the onset and decreased the degree of arthritis.

PATHOLOGY OF POLYARTHRITIS IN RATS

This polyarthritis in the rat is a purulent process which goes on to eventual fibrous and bony ankylosis (Figs. 125 and 126). Abscesses are also to be



Fig 125 Albino rat showing extensive polyarthritis one week following the intraperitoneal injection of 2 cc of broth culture of L_4 strain of pleuropneumonia-like organisms

found in the peritoneal cavity and the lungs In the mouse the pathologic changes are not purulent, but also go on to ankylosis.[1] The possibilities of therapeutic trials in the polyarthritis of rodents include: (*a*) the discovery of agents which act as well as gold without undesirable side effects for possible therapeutic trials in man, (*b*) the discovery of compounds or environmental conditions which may aggravate the arthritis thereby giving some lead as to etiology, and (*c*) discovery of possible combinations of agents which may alter the course of the experimental polyarthritis.

METHODS

Our studies have been confined to rats since we have been unable to reproduce the mouse arthritis after repeated trials over a three-year period

using numerous strains of mice and like strains from different institutions The microbe used in these studies was originally isolated in 1942 by Preston and was obtained from Dr Dienes of Boston It has been carried in culture using the media described by Tripi and Kuzell[19] which consists of 3 0 gm. of Difco dehydrated yeast extract 7 0 gm of Difco nutrient broth concentrate, 10 0 gm. of tryptose phosphate broth concentrate, and 2 0 gm of dextrose, C P., added to 1 liter of distilled water To this 0.5 gm agar is added for broth and 2.0 per cent agar for solid media Adjustment of pH is made to produce a final value of 8 0 after autoclaving Using aseptic pre-



Fig 128 Photomicrograph (×100) showing section of the ankle joint of an albino rat three weeks following the intraperitoneal injection of 2 cc of broth culture of L4 strain of pleuropneumonia-like organisms

cautions, 20 per cent normal unpreserved horse serum is added to this medium The rats were infected by injection of 2 cc of broth culture of L4

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fection and became worse for seven to ten days thereafter before spontaneous improvement became evident Occasionally deaths resulted from the infection. Similar results were obtainable by use of 0 2 cc of the broth culture given intravenously, but when large numbers of animals were used this method proved to be too time-consuming and did not produce any higher incidence of joint involvement In scoring the effect of the various agents tested, three factors were considered: percentage incidence of ar-

thritis in each group, percentage survival, and the average arthrogram score for the group Since the arthritis-producing properties of the microbe sometimes varied from one culture to another each test group had a control made simultaneously. To compute the arthrogram score a numerical value of 4 was assigned to each front leg and 5 to each hind leg and then the highest value of the extent of joint involvement during a three-week period was recorded for each animal [16] The average score for the group was determined by adding the highest score attained by each individual rat and dividing by the number of rats in the group irrespective of the percentage incidence of arthritis for the group. Comparisons were made with controls and with infected rats medicated with gold salts. When substances were mixed in the food or drinking water their administration began the day of infection and continued for the duration of the experiment When substances were injected by stomach tube they were begun at the time of infection and continued for variable periods as indicated in the accompanying tables.

RESULTS

Table 62 shows the agents tried for preventive effect on the polyarthritis It will be noted that aurothioglucose (Solganol-B), sodium aurothiosulfate, and aureomycin given at the time of infection prevented the development of the arthritis. Aurothioglycoanalid (Lauron) was also effective in pre- [illegible] which had received a single [illegible] A [illegible] y colchicine, [illegible] sodium benzoate (Cupralène), pentaquine (SN-13276 [illegible] hexavanadate, streptomyc [illegible] sulfamerazine, desiccated thyroid, cystine, and the anterior pituitary-like hormone chorionic gonadotrophin (Follutein)

When the arthritis was allowed to develop aureomycin given by injection (100 mg per kilogram) caused the arthritis to subside within forty-eight hours [17]

In the course of these trials a large number of substances were found to be of no demonstrable benefit in preventing the arthritis, but on the other hand did not appear to aggravate it These substances or procedures included *olive oil (1 cc per kilogram, intramuscularly)*, hesperidin chalcone (2 per cent in diet), rutin (0 5 per cent in diet), sodium gentisate (10 gm. [illegible] daily for [illegible] rine [illegible] sub-cutaneously), phenobarbital (0 1 per cent in diet), [illegible] 0 01 per cent in diet), thyroidectomy, isopropyl alcohol (0.1 per cent in water), increased heat, ultraviolet light, exposure to cold, 3-*o*-toloxyl-1,2-propanediol (Tolserol) (2 per cent in water), Diasone (0 75 per cent in diet), progesterone (1 mg. per kilogram for four days, *intramuscularly*), *desoxy*-corticosterone acetate (0 5 mg for four days, intramuscularly), ketohydroxy estratriene (Theelin) (2 mg per kilogram for four days, intramuscularly), and Chloromycetin (10 mg per kilogram for four days, intramuscularly, and 50 to 100 mg *per kilogram for three days*, by intubation).

Table 63 shows agents which made the arthritis worse. These include Sobisminol, xanthium (cocklebur extract), 2,3-dimercaptopropanol (BAL),[18]

Table 62. Agents with Preventive Effects on Experimental Polyarthritis of Rats

AGENT	ROUTE OF ADMINISTRATION	DOSE	MEDICATED RATS				UNMEDICATED RATS (CONTROL)			
			No. of rats	Incidence of arthritis	Survival rate	Av. arthrogram score	No. of rats	Incidence of arthritis	Survival rate	Av. arthrogram score
				%	%			%	%	
Gold sodium thiosulfate	I.M.*	8 mg./kg. 3 days	20	15	100	0.35	20	35	100	0.9
Solganol-B	I.M.	33.7 mg./kg	10	0	90	0	10	50	90	1.6
Solganol-B	I.M.	67 mg./kg	26	15	100	0.31	26	84	100	3.7
Aureomycin	Diet	0.3%	20	0	100	0	20	55	100	1.7
"	Diet	0.1%	20	0	100	0	20	75	94	1.5
"	Diet	0.05%	26	5	100	0.07	26	84	100	3.7
"	Intubation	50 mg./kg 2 days	10	20	100	0.2	10	80	90	3.1
"	Intubation	20 mg./kg 2 days	10	20	100	0.4	10	80	90	3.1
"	Hypo	100 mg./kg 1 day	10	20	100	0.2	10	80	90	3.1
Cupraline	I.M.	5 mg./kg 18 doses	20	95	70	6.45	20	94	45	6.95
"	I.M.	20 mg./kg 7 doses	20	70	100	2.25	20	65	100	2.9
"	I.P.†	5 mg./kg 18 doses	20	80	90	3.3	20	60	100	2.5
Pentaquine	Water	50 mg./l	10	10	90	0.8	26	67	100	2.5
Streptomycin	Hypo	10,000 U ×2–3 days	10	20	100	0.5	10	80	90	2.9
Streptomycin & Vitamin D	Hypo	5000 U (S) & 50,000 U (D)/kg	10	60	100	1.2	10	80	90	2.9
Salazopyrin	Diet	0.5%	20	66	95	2.1	20	77	64	2.2
Sulfamerazine	Water	300 mg./l	15	42	100	1.56	26	67	100	2.5
Sulfadiazine	Water	250 mg./l	15	57	100	1.7	26	67	100	2.5
Colchicine	Hypo.	0.0065 mg 4 days	10	30	100	1.1	10	60	100	2.2
Thyroid	Water	500 mg./l	10	50	100	1.1	10	60	100	2.2
Cystine	Diet	1%	10	20	90	1.0	20	65	100	1.7
Chorionic gonadotrophin	I.M.	10 U 4 days	10	20	100	0.2	20	65	100	1.7

* Intramuscular † Intraperitoneal

Table 63 Agents which Aggravated Polyarthritis of Rats

Agent	Route of adminis-tration	Dose	Medicated rats: Number of rats	Medicated rats: Incidence of arthritis	Medicated rats: Survival rate	Medicated rats: Average arthrogram score	Unmedicated rats (control): Number of rats	Unmedicated rats (control): Incidence of arthritis	Unmedicated rats (control): Survival rate	Unmedicated rats (control): Average arthrogram score
				%	%			%	%	
Sobisminol	Water	0 00038%	10	70	90	2 3	10	60	90	1 7
Xanthium	Diet	1 28 gm /kg food	20	70	100	2 5	20	70	100	1 7
Xanthium	Hypo	10 mg /kg 3 days	20	77	85	3 0	20	65	100	1 95
BAL*	I M †	5 mg /kg 5 days‡	90	73	89	2 86	80	55	95	1 83
PABA§	Diet	0 7%	20	80	95	3 5	20	80	95	2 6
PABA plus sodium salicylate	Diet Water	0 7% 0 2%	20	95	95	4 8	20	80	95	2 6
PABA plus sodium gentisate	Diet Water	0 7% 1 0%	20	85	100	3 75	20	80	95	2 6
Oxophenarsine	Hypo	10 mg /kg	20	90	90	3 15	20	80	94	2 45
Rutin plus ascorbic acid	Diet Water	0 5% 412 mg /l	10	40	50	1 7	10	66	100	2 2
Pituitary gonado-trophin	I M.	0 8 U	10	77	100	2 0	20	49	90	1 1

* 2, 3-Dimercaptopropanol
† Intramuscular
‡ Then once weekly for four weeks.
§ Para-aminobenzoic acid

para-aminobenzoic acid, para-aminobenzoic acid plus sodium salicylate, and para-aminobenzoic acid plus sodium gentisate, oxophenarsine, rutin plus ascorbic acid, and pituitary gonadotrophin. Roentgen therapy (100 r) given after development of arthritis caused increased joint involvement as compared with the controls The serum from rats convalescent from the infection also aggravated the arthritis In a previous study it was shown that thiouracil increased the incidence and severity of the arthritis [19]

COMMENT

Admittedly this approach to the problem of arthritis leaves much to be desired, and the most that we can obtain from such methods is an indication that certain substances or combinations of substances may act as well as gold compounds in preventing and curing the rat arthritis Among the agents found to be of benefit in this experimental polyarthritis were several which may be worthy of clinical trials Aureomycin, which showed both preventive and curative effects, has thus far been disappointing in preliminary clinical trials in typical rheumatoid arthritis, but has produced a striking cure in a case of Reiter's syndrome [17] Favorable clinical therapeutic results have been presented by Svartz[20] for Salazopyrin, and by Forestier[21] for Cupraléne. To our knowledge, no clinical trials have been made with cystine, pentaquine (SN-13276), sodium hexavanadate, and the combination of streptomycin and vitamin D Trials with these substances in rheumatoid arthritis may be worth while Comroe[22] reports that clinical trials with chorionic gonadotrophin have been without benefit, but this may be worth reevaluation clinically It is of interest that the antimalarial [illegible] dosage [illegible] the [illegible] e of rheumatoid arthritis Although desiccated thyroid, sulfadiazine, and sulfamerazine are of slight beneficial effect in the rat polyarthritis, we know of no reports of their benefit in rheumatoid arthritis

[illegible] the growth of these microbes easier from the body fluids and secretions of man

BAL [illegible] has been advocated as a remedy [illegible] the growth of the microbe in vivo

In addition to making further chemotherapeutic trials in this polyarthritis of rats and mice, further efforts should be made to isolate the pleuropneumonia-like organism from man by newer approaches or improved methods Perhaps the use of some of the agents which aggravate the rat polyarthritis will aid in facilitating this search

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ABSTRACT

POSSIBLE RELATIONS BETWEEN RHEUMATIC FEVER AND ALLERGY EXPERIMENTAL STUDY IN THE RABBIT

ANIBAL RUIZ-MORENO, RODOLFO SAMMARTINO AND MANUEL LITTER

Numerous controlled experiments were carried out in rabbits sensitized to normal horse serum The shock dose, or injection, in single or multiple doses of 0 5 cc, was given intra-articularly in the right knee, the left knee being injected with similar [illegible] organs were studied

tions of saline may act as a weak sensitizing agent. The articular, cardiac and pulmonary lesions observed in these experiments are analogous to similar lesions encountered in rheumatic fever

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